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ORGANIC SEMINAR ABSTRACTS

1967-68

Semester II

Department of Chemistry and Chemical Engineering

University of Illinois



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II Semester 1967-68

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## THE CHEMISTRY OF CYCLOOCTATETRAENE ANIONS

Reported by Jerome J. McDonald

February 22, 1968

The Hückel Rule of aromaticity states that a carbocyclic system with a closed shell of  $4n + 2$   $\pi$ -electrons should have a high degree of resonance stabilization. Having only eight electrons, cyclooctatetraene (COT) has been demonstrated to have a non-planar stereochemistry with little or no resonance stabilization.<sup>1</sup> The Hückel Rule would predict, however, that the addition of two electrons to the electron cloud of COT would form a stable system. This seminar will present evidence that COT takes up two electrons at a metal electrode, that there is an equilibrium between the radical anion and that dianion greatly displaced toward the dianion, and that the nucleophilic reactions of the dianion illustrate the transitory existence of the monoanion.

## POLAROGRAPHIC EVIDENCE

Cyclooctatetraene in 50% ethanol solution is smoothly reduced. The well-defined polarographic wave has a halfwave potential of -1.51 volts vs. a saturated calomel electrode and corresponds to a single-step reduction involving two electrons.<sup>2</sup> The products of this reduction have been identified as a mixture of 1,3,5- and 1,3,6-cyclooctatriene.<sup>3</sup> In a more extensive study by Katz and co-workers,<sup>4</sup> a single well-formed wave of halfwave potential -1.12 volts vs. a mercury pool corresponding to the reversible addition of two electrons to COT in 96% dioxane was observed. Oscillopolarography of COT in 96% dioxane showed a single peak with approximately the same half-peak potential on the cathodic half cycle as the halfwave potential on the d.c. polarogram. No peak corresponding to reoxidation on the anodic half cycle was seen until the triangular wave frequency was increased and the d.c. bias was shifted to confine the cathodic half cycle to the foot of the wave. These observations suggest the conclusion that the reduction of COT proceeds through simple reversible addition of two electrons followed by a rapid reaction of the dianion with the solvent.<sup>4</sup>

Polynuclear aromatic hydrocarbons in aprotic media show polarograms of two waves, each corresponding to a reversible one electron reduction. The second reduction is followed by a rapid reaction of the dianion with the solvent.<sup>5</sup> It is recognized that electronic repulsion decreases the facility with which the second electron transfer occurs.<sup>6</sup> In contrast to these results, the transfer of the second electron to COT is very facile. The coulombic repulsion of the second electron must be very much less than the energy barrier to the addition of the first electron. This barrier must be the compressional energy of making the stable "tub" form of COT planar. Once the planar form is attained, the added electrons go into non-bonding instead of antibonding orbitals, completing the aromatization of the COT dianion.

## SPECTROSCOPIC EVIDENCE

Katz first observed the NMR spectrum of the cyclooctatetraene dianion<sup>7</sup> and the ESR spectrum of cyclooctatetraene radical anion.<sup>8</sup> The NMR spectrum of cyclooctatetraene in the THF solution containing two molar equivalents of either lithium or potassium shows a single sharp peak insignificantly removed from the resonance of cyclooctatetraene. When potassium is first added to the THF solution, the COT peak gradually decreases in intensity, all the while remaining sharp (half width < 1 cps), and gradually disappears into a growing broad (~ 18 cps) peak. This new absorption, which is typical for exchange broadening, gradually forms the sharp (< 1 cps) resonance of the COT dianion, only equal in intensity to the original COT resonance once two molar equivalents of potassium have dissolved. Since the COT resonance remains sharp until disappearance, it is not involved in the exchange process. The solvent resonance also remains sharply defined throughout the addition, showing that a large concentration of the paramagnetic radical anion is never reached. The broadening must be due to electron exchange between the dianion and the radical anion, the proton resonance of which occurs nine megacycles out of range.

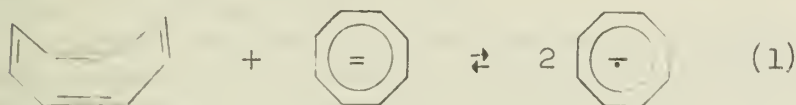
Increased proton shielding from the addition of electrons to COT would be





expected to move proton resonance to higher field. This tendency is counteracted by the aromatization of the COT ring. The diamagnetic ring current then induced in the dianion deshields the protons,<sup>9</sup> and the net effect on resonance position happens to be zero. It is apparent that the lack of electron exchange between COT and its anion, and the facile exchange between the anions themselves indicates they must be of similar structure, unlike that of COT. It is expected that the anions are planar. Recognition of the low concentration of the monoanion means that equilibrium 1 is displaced to the left. The concentration of the radical anion has

been measured, and the equilibrium constant for the reaction of equation 1 calculated as  $10^{-9}$  for a corresponding free energy change of 11 kcal/mole.<sup>10</sup>

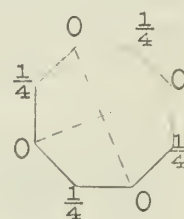
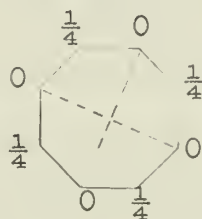


Lithium samples of COT in THF best exhibit the nine line spectrum of the COT dianion with a proton hyperfine splitting constant of 3.209 gauss.<sup>8,10</sup> Up to 71% of the total radical anion concentration in a sample of relative stoichiometric concentration 1:80 of lithium to COT was complexed with lithium ions, as shown by the fine structure from the  $\text{Li}^7$  splitting of 0.24 gauss with a line width of 0.24 gauss. There was no evidence for any uncomplexed COT radical anion in the spectrum with a  $\text{Na}^{23}$ -THF mixture. The  $\text{Na}^{23}$  splitting was 0.9 gauss with a line width of 0.8 gauss. The line width depends on the rate of electron exchange between the radical and the anion. The  $\text{K}^{39}$ -THF sample shows the largest line broadening, in agreement with NMR studies.<sup>7</sup> The ESR spectrum of a stoichiometric composition of 1:1 of potassium to COT is a single line of 6 gauss width. Only when the K:COT ratio is about 1:10 can the spectrum be resolved into peaks 3.2 gauss apart, and even then the line width is 1.3 gauss, much larger than in the  $\text{Li}^7$ -COT spectrum. Coupled with the lack of electron exchange with the neutral COT molecule observed in NMR studies,<sup>7</sup> this facile electron exchange between the anions indicates their similar planar character as distinct from the "tub" form of COT itself.

It has been predicted<sup>11</sup> that the planar regular octagonal structure of COT would be subject to Jahn-Teller distortion to relieve the degeneracy of the non-bonding orbital. However, MO calculations on the COT radical anion show that the broadening of the ESR resonance peaks due to this distortion would be only 0.08 gauss, and thus too small to account for the observed broadening.<sup>12</sup>

The ESR spectra of the monomethyl, ethyl, n-propyl, and n-butyl-COT radical anion also support the planar structure for the radical anion.<sup>13</sup> In general, all the spectra can be analyzed as resulting from a quartet due to three equivalent ring protons, a quartet for the methyl, or a triplet for the ring-bonded methylene protons. The splitting constants are as shown. The degenerate, non-bonding orbitals

1	R	$a_1$	$a_2$	$a_3$
	H	5.1	1.6	4.8
	$\text{CH}_3$	2.5	1.9	4.5
	$\text{C}_2\text{H}_5$	2.6	1.9	4.5
	$\text{C}_3\text{H}_7$	2.6	1.9	4.5



of planar COT into which the ninth electron goes are illustrated with their electron densities. The substituent acts to remove this degeneracy and, since alkyl groups are electron repelling, two of the three  $\pi$ -electrons in the non-bonding orbitals of the radical anion must go into an orbital having a node at the substituent position. This leaves the unpaired electron occupying the orbital having a density of  $\frac{1}{4}$  at the substituent position. Thus the three other equivalent positions on the ring would be expected to have the larger ring proton coupling constant. Since there is another ring coupling constant the two orbitals must be mixed by vibronic coupling.<sup>13</sup> The smaller proton coupling constant of the  $\text{C}_2$ - $\text{C}_4$  substituents is due to their restricted rotation caused by steric hindrance having its origin in the large ring bond angle.<sup>14</sup>

The ESR spectrum of monodeuterated COT lends similar support to the aromaticity of the radical anion. The spectrum consists of eight triplets corresponding to





seven equivalent protons of  $a_H 3.20$  gauss and a splitting constant for deuterium of 0.50 gauss.<sup>15</sup> The ring protons would be equivalent if the ground state consisted of two different structures of alternating long and short carbon-carbon bonds.

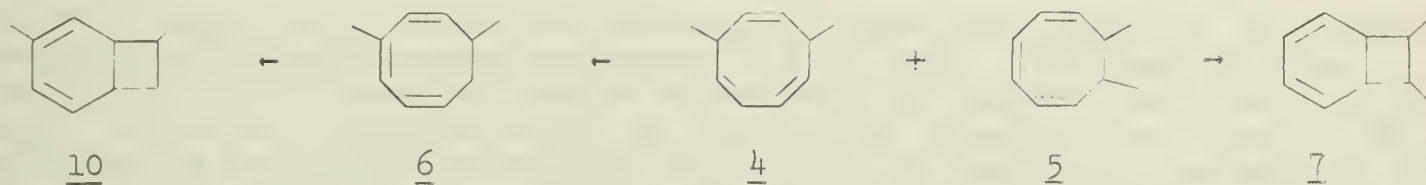
#### PROTONATION OF COT DIANION

The earliest known reactions of the cyclooctatetraene dianion involve proton sources. Reppe<sup>16</sup> quenched the adduct of lithium and cyclooctatetraene with water to get a triene formulated as 1,3,6-cyclooctatriene. Carbonation of the organolithium intermediate yielded a dicarboxylic acid assigned the structure of 2,4,7-cyclooctatriene-1,6-dicarboxylic acid.

Cope<sup>17</sup> studied the protonation of disodium cyclooctatetraenide generated in liquid ammonia with ammonium chloride and showed that the product was a 1:1 mixture of 1,3,6- and 1,3,5-cyclooctatriene (1 and 2). He also showed<sup>18</sup> that a thermal equilibrium of 2 with bicyclo[4.2.0]octa-2,4-diene(3) could be achieved with a ratio of 85 to 15 in favor of 2.  $COT^{=}$  generated by reaction of COT with triphenylmethyl sodium has been decomposed with water to yield 2.<sup>19</sup>

#### NUCLEOPHILIC REACTION WITH METHYL IODIDE

Bak and Conrow<sup>20</sup> have shown that dialkali cyclooctatetraenide ( $COT^{=}$ ) reacts as a nucleophile with methyl iodide. The reaction of methyl iodide with dipotassium  $COT^{=}$  yields an isomeric mixture composed of 40% 5,8-dimethyl-1,3,6-cyclooctatriene (4), 47% 7,8-dimethyl-1,3,5-cyclooctatriene (5) and 13% 3,8-dimethyl-1,3,5-cyclooctatriene (6). Both 4 and 6 were isolated. The isomer 5, presumably because of



extensive dimerization through its valence tautomer 7,8-dimethylbicyclo[4.2.0]octa-2,4-diene (7), was not isolated in a pure state but was identified by its ozonolysis products meso- and dl-2,3-dimethylsuccinic acid.

When the mixture of cyclooctatriene 4, 5 and 6 was heated to 150°, both 3,4-dimethylcyclobutane-1,2-dicarboxylic acid (8), and 3-methylcyclobutane-1,2-dicarboxylic acid (9) were identified as ozonolysis products. These cyclobutanedicarboxylic acids must result from 7 and 3,8-dimethylbicyclo[4.2.0]octa-2,4-diene (10), which are valence tautomers of 5 and 6. According to the rules governing the stereochemistry of electrocyclic reactions,<sup>21</sup> both 8 and 9 should be cis-1,2-dicarboxylic acids, but this was not determined in this study. Cope, however, isolated cis-1,2-cyclobutanecarboxylic acid from the <sup>o</sup>z<sup>a</sup>olysis of 3.<sup>18</sup> Thus, a disrotatory mechanism is operable in the tautomerization of 2 to 3, and probably also in the tautomerization of 5 to 7, and of 6 to 10.

Cyclooctatriene 6 is not a direct product of the reaction of  $COT^{=}$  with methyl iodide, but results from the thermal rearrangement of 4 via a 1,5-hydrogen shift. A pure sample of 4 is equilibrated at 100° to a mixture of 70% 4 and 30% 6 (Fig. 1).

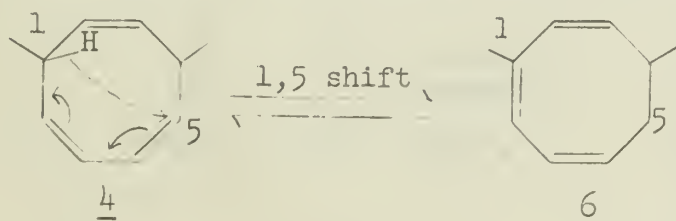


Fig. 1

Roth has demonstrated the exclusiveness of 1,5-hydrogen shifts in deuterium-labeled 1,3,5-cyclooctatetraene.<sup>22</sup> The rearrangement of 7,8-dideuterio-1,3,5-cyclooctatriene (11) via 1,3-hydrogen shifts would lead to a statistical distribution of the two deuterium atoms over all positions on the carbon skeleton. Rearrange-

ment by means of 1,5-hydrogen shifts should lead to distribution of deuterium only over positions 3, 4, 7 and 8 (Fig. 2). NMR analysis of the dimethyl acetylene dicarboxylate adduct of the 1,3,5-cyclooctatriene resulting from equilibration at 225° confirms predicted statistical distribution of two deuterium atoms over four



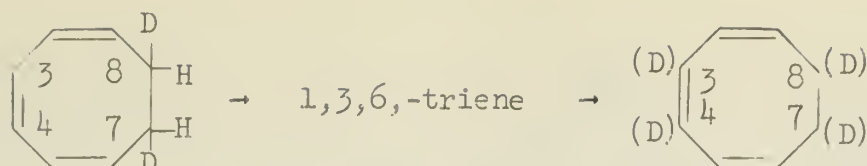


Fig. 2

carbon atoms resulting from 1,5-hydrogen shifts.

These results seem to indicate that dipotassium  $\text{COT}^=$  reacts with methyl iodide as a dianion to form both the 1,4- and the 1,2-adducts 4 and 5. Attempts to isolate an intermediate monoalkylation product yielded only a mixture of the unsubstituted trienes 1 and 2.<sup>20</sup> Thus the initial reaction between the dianion and methyl iodide is slow and the subsequent reaction with methyl iodide quite rapid. In addition to the dianion, the first molecule of methyl iodide has to overcome the resonance stabilization of the 10  $\pi$ -electron system. The resulting monoanion then reacts immediately with a second molecule of methyl iodide. Both the 1,4- and the 1,2-adducts are formed in nearly equal amounts, reflecting an equal distribution of charge in the monoanion over four carbons, two of which are  $\alpha$  to the methyl group first introduced, and two of which are  $\gamma$  to the methyl group (Fig. 3). The relative



Fig. 3

amounts of meso- and dl-dimethylsuccinic acids obtained from ozonolysis of 5 indicates that the cis and trans isomers are present in a 4:1 ratio. This lack of stereospecificity is to be expected from the mechanism of the reaction and in view of the steric interaction the second methyl group encounters in each of the isomers. The methyl groups are eclipsed in the cis, diequatorial form and one of the methyl groups is axial in the trans form, leading to an interaction with transannular hydrogens (Fig. 4). In contrast, the NMR spectrum of the 5,8-dimethyl-1,3,6-isomer shows that

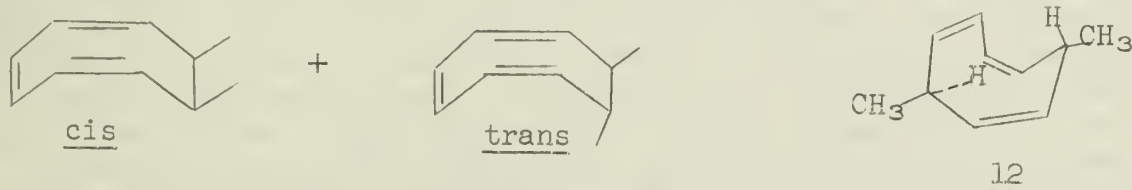
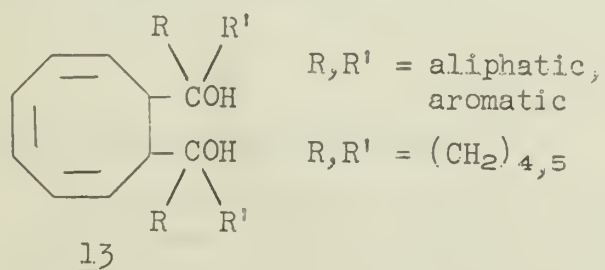


Fig. 4

it is present entirely as the diequatorial, trans form (12). Axial methyl groups would have strong interaction with the  $\pi$ -electron cloud of the transannular double bond.

#### REACTIONS WITH ALDEHYDES AND KETONES

It has been reported<sup>23</sup> that dilithium  $\text{COT}^=$  reacts with various aliphatic, cyclic, and aromatic ketones to form 7,8-disubstituted-1,3,5-cyclooctatrienes of the type 13 in 70% yield. In addition, trienes of type 13 where  $\text{R}, \text{R}'$  is aliphatic undergo dehydration catalyzed by *p*-toluenesulfonic acid to 2,2,5,5-tetrasubstituted-3,4-cyclooctatrienotetrahydrofuran derivatives.<sup>23</sup>

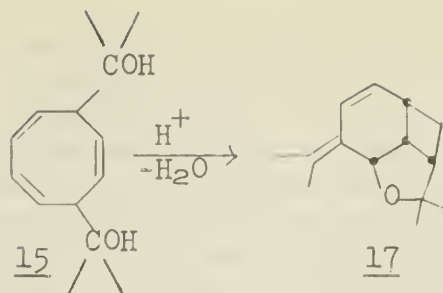
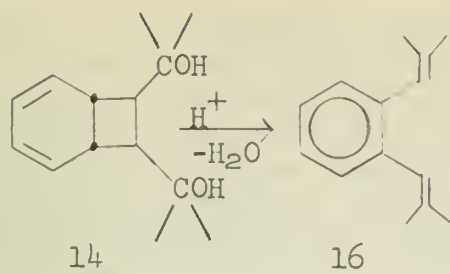


Cantrell and Shechter have made a systematic investigation of the products of the reaction of dilithium  $\text{COT}^=$  with aldehydes and ketones and have found that  $\text{COT}^=$  reacts both as a 1,2- and a 1,4-dicarbocationic reagent.<sup>24</sup> In the reaction with acetone an inseparable mixture of 7,8-bis(2-hydroxy-2-propyl)bicyclo[4.2.0]octadiene (14) and 5,8-bis(2-hydroxy-2-

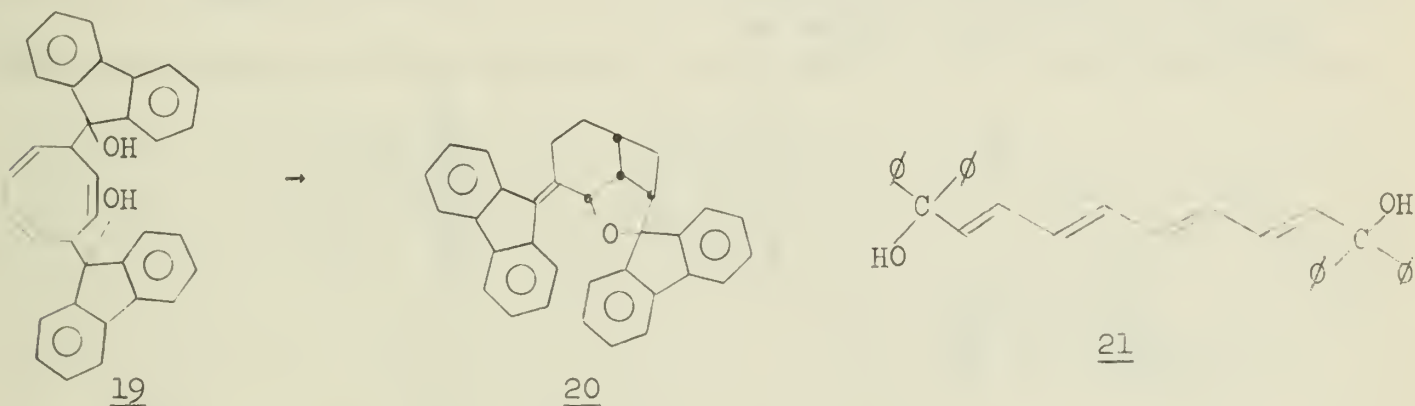
propyl)-1,3,6-cyclooctatetraene (15) is formed. Dehydration of the mixture of 14 and 15 with a catalytic amount of *p*-toluenesulfonic acid yielded *o*-bis(2,2-dimethylvinyl)benzene (16) and 3,3-dimethyl-9-isopropylidene-2-oxa-7-tricyclo[4.3.1.0]decene (17) which could be isolated pure. Both dehydration products arise from reasonable





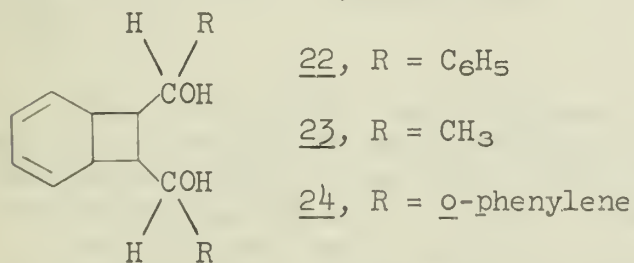


mechanistic pathways and are conclusively identified by their analyses, NMR, UV, and IR spectra. The reaction of  $\text{COT}^-$  with benzophenone yields 5,8-bis( $\alpha$ -hydroxybenzhydryl)-1,3,6-cyclooctatriene (18) which is completely analogous to the 1,4-adduct 15. Acid-catalyzed dehydration of 18 yields a tricyclic compound analogous to 17 with the methyl groups replaced by phenyl groups.  $\text{COT}^-$  formed only a 1,4-adduct (19) with fluorenone which is dehydrated to a structure believed to be 20.



The other product of the reaction of  $\text{COT}^-$  with benzophenone is the polyene 1,1,10,10-tetraphenyl-2,4,6,8-tetraene-1,10-diol (21). The principal reason for ring opening is the relief of steric strain. Bulky, diequatorial (*cis*)  $\alpha$ -hydroxybenzyl groups on the initial 1,2-adduct are eclipsed. Should one group be axial (*trans* to the other), it encounters transannular interaction with the  $\pi$ -system. The formation of the bicyclo[4.2.0]octadiene eliminates the transannular interaction of an axial group and lessens the interaction of *cis* groups by widening the dihedral angle between them. Also, the polyene is more conjugated than its tautomer.

Benzaldehyde, acetaldehyde, and *o*-phthalaldehyde form the products 7,8-bis( $\alpha$ -hydroxybenzyl)bicyclo[4.2.0]octadiene (22), 7,8-bis( $\alpha$ -hydroxyethyl)bicyclo[4.2.0]octadiene (23) and 4,5-benzotricyclo[6.4.0.0]dodeca-9,11-diene-3,6-diol (24) all derived from their 1,2-adducts.



Acetaldehyde addition product 23 was identified in mixture with its isomer, the 1,4-adduct 5,8-bis( $\alpha$ -hydroxyethyl)-1,3,6-cyclooctatriene by appropriate comparison of spectra. Attempted dehydration of the mixture led to the formation of 7-( $\alpha$ -hydroxyethyl)-1,3,5-cyclooctatriene. Acid-catalyzed dehydration of 24 yielded 2-phenylnaphthalene.

#### REACTIONS WITH ACYL HALIDES

The first reported products from the reaction of dilithium  $\text{COT}^-$  with acyl chlorides were reported to give 7,8-diacyl-1,3,5-cyclooctatrienes.<sup>23</sup> Under similar reaction conditions, Cantrell and Shechter have isolated *trans*, *cis*, *cis*, *trans*-3,5,7,9-dodecatetraene-2,11-dione (25), *syn*-9-hydroxy-9-methylbicyclo[4.2.1]nona-2,4,7-triene (26), *syn*-9-acetoxy-9-methylbicyclo[4.2.1]nona-2,4,7-triene (27), and *syn*-9-acetoxy-9-methylbicyclo[6.1.0]nona-2,4,6-triene (28) from the reaction of dilithium  $\text{COT}^-$  with excess acetyl chloride.<sup>25</sup> According to the Woodward-Hoffman



rules for electrocyclic reactions,<sup>21</sup> the thermal opening of a cyclooctatriene should be a conrotatory process. In order for the terminal double bonds of 25 to be trans, the substituents on what must be its precursor (7,8-diacetyl-1,3,5-cyclooctatriene) must be trans to each other. Compounds 26 and 27 must result from intra-molecular reaction at C-4 of the eight-membered ring of the intermediate monoacetyl monoanion. Both 26 and 27 can be transformed into the same saturated bicyclic alcohol (29). The identical alcohol is synthesized from methylmagnesium iodide and bicyclo[4.2.1]nonan-9-one (30). Since the Grignard reagent must

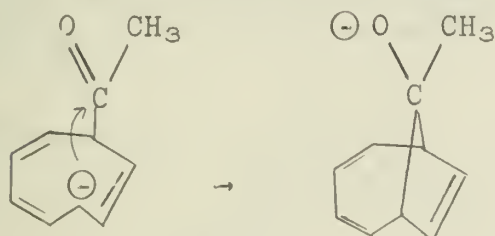
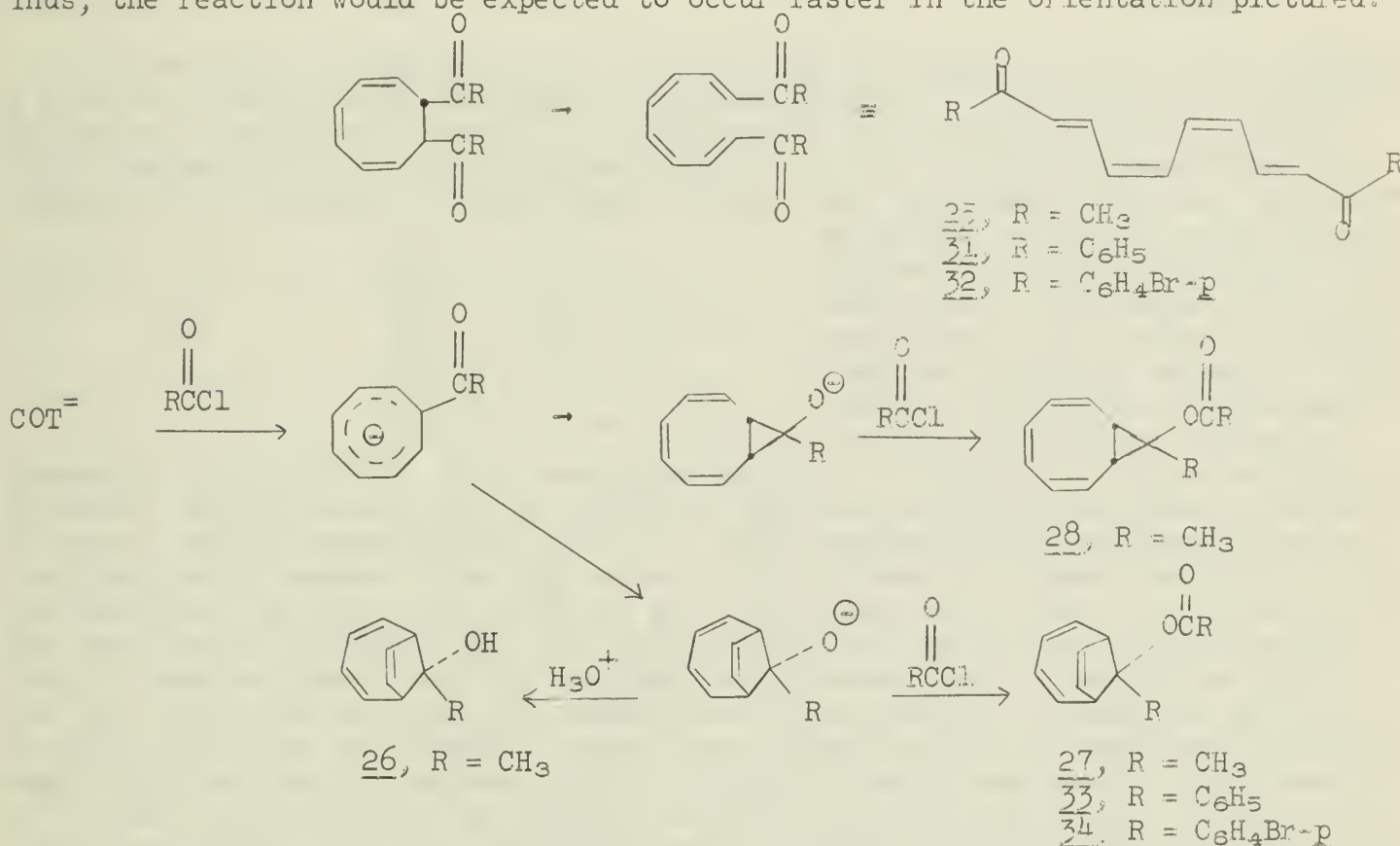


Fig. 5

approach from the less hindered side of 30, the syn geometry of the hydroxyl in 29, and thus in 26, and of the acetoxy in 27 seems assured. This result can be predicted from the geometry of the intermediate monoacetyl monoanion (Fig. 5). The stereochemistry must be as shown because of the larger effective size of the methyl relative to the oxygen.

Thus, the reaction would be expected to occur faster in the orientation pictured.



The cyclopropyl ring of 28 must be cis-fused because of the mechanism of attack of the C-2 carbon of the intermediate monoacetyl monoanion. The stereochemistry of the acetoxy group is not known for certain, but application of the same arguments used for 26 and 27 make it seem likely that it is syn to the larger ring.

Both benzoyl and *p*-bromobenzoyl chloride react with dilithium COT<sup>-</sup> to form only the polyenes 31 and 32, and the bicyclo[4.2.1]systems 33 and 34. The same arguments for their formation and stereochemistry apply as in the case of acetyl chloride. The reaction of phthaloyl dichloride with dilithium COT<sup>-</sup> give the lactone of 9-(2-carboxyphenyl)-9-hydroxybicyclo[6.1.0]nonatriene as the only isolable product.

#### REDUCTION REACTIONS

First pointed out by Katz to be a potent reducing agent,<sup>13</sup> COT<sup>-</sup> reduces benzil, 9,10-phenanthrenequinone and the polyene 31. Benzil is reduced to benzoin probably by the transfer of two electrons to benzil to yield cyclooctatetraene and dianion 35, which is then diprotonated to yield benzoin.<sup>24</sup> In contrast, the weaker electron acceptor 9,10-phenanthrenequinone accepts only one electron. The only product

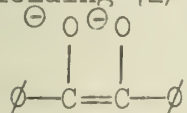




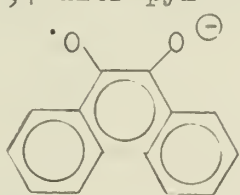


isolated, probably radical anion 36, is a pyrophoric powder which upon hydrolysis and acidification yields the starting quinone.<sup>24</sup> When benzoyl chloride reacts with dipotassium COT<sup>-</sup>, polyene 31 is produced along with some trans-1,10-dibenzoyloxy-1,10-diphenyldeca-1,3,5,7,9-pentaene (37). The formation of 37 seems to involve reduction of 31 to a dianion with subsequent O-acylation by benzoyl chloride.<sup>25</sup>

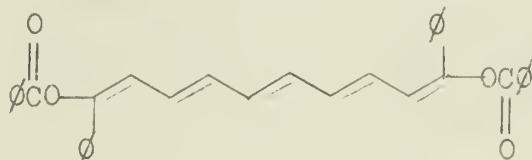
Other reductions involve the dimerization of cations. Dipotassium COT<sup>-</sup> reacts exothermically with 2,4,6-trimethylpyrylium fluoroborate to yield 38 in 54% yield.<sup>26</sup> The reaction of the same reagent with tropylium fluoroborate is also exothermic, yielding 72% of 7,7-ditropyl.<sup>27</sup>



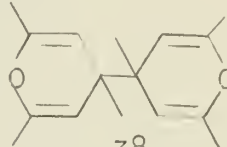
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36



37



38

In reacting with gem-dihalides, dipotassium COT<sup>-</sup> seems to reduce the halide to a divalent carbene which then adds to cyclooctatetraene. Products of the reaction of COT<sup>-</sup> with methylene chloride,<sup>28</sup> chloroform,<sup>28</sup> dichloromethyl methyl ether,<sup>28</sup> carbon tetrachloride,<sup>28</sup> 1,1-dichloroethane<sup>29</sup> and 1,1,1-trichloroethane<sup>29</sup> are the 9-substituted-bicyclo[6.1.0]nonatrienes 39-44.



- 39, R = R' = H
- 40, R = Cl, R' = H
- 41, R = OCH<sub>3</sub>, R' = H
- 42, R = R' = Cl
- 43, R = H, R' = CH<sub>3</sub>
- 44, R = Cl, R' = CH<sub>3</sub>

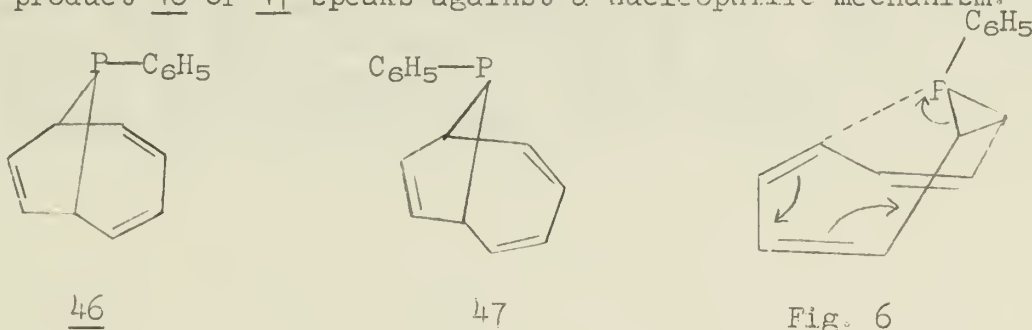
The syn isomer of 40 was isolated<sup>29</sup> as the major product of an isomeric mixture of 9-chloro-bicyclo[6.1.0]nonatrienes synthesized from cyclooctatriene by the method of Closs used for producing carbenes.<sup>30</sup> The reductive mechanism is reasonable in view of the known reductive

properties of COT<sup>-</sup>.<sup>24-27</sup> Also, methylene chloride is unreactive toward S<sub>N</sub>2 displacement and replacement of its hydrogens by either methyl or chlorine is expected to have a further deactivating effect.<sup>31</sup> What determines the stereochemistry of the products is unknown. The syn isomer 43 would seem to be more sterically hindered than the anti-isomers 40 and 41. The alkali metal seems to have no effect. The reaction of dilithium COT<sup>-</sup> with chloroform<sup>28</sup> also yields the anti-isomer 40. There is some evidence that the inorganic salt present in the reaction mixture has some effect on the isomeric composition of the products. Using the method of Closs<sup>30</sup> to prepare chloromethyl carbene from methyllithium and methylene chloride, Katz found that the products of addition to cyclooctatetraene were a small amount of 43, and a 4:1 ratio of the syn:anti mixture of 40 when the methyl lithium contained lithium iodide.<sup>29</sup> When the methyl lithium contains lithium bromide, the only isolable product is a small amount of 43. In all cases lithium chloride is present. These results suggest that the carbenes are complexed by alkali halides, as has been observed before.<sup>32</sup> More indicative results could perhaps be attained by including lithium bromide or iodide in the solution of COT<sup>-</sup> prepared for reaction with chloroform.

Sulfur dichloride simply oxidizes dipotassium COT<sup>-</sup> to give a good yield of cyclooctatetraene. Dichlorophenylphosphine, however, forms the 1,2-adduct 9-phenyl-9-phosphabicyclo[6.1.0]nonatriene (45)<sup>33</sup> which was identified by analysis and NMR with extensive decoupling. Upon rearrangement in chloroform solution at 70°, 45 yields the bicyclo[4.2.1]nonatriene 46, which is in turn epimerized to 47 at higher temperature or with acid catalysis. By interpreting the chemical shifts of the olefinic protons in terms of shielding by the phenyl group, its orientation can be assigned as in 46 and 47. Since both 45 and 46 are homogeneous according to NMR spectra, the rearrangement of 45 to 46 must be stereospecific. This in turn means that the phenyl group of 45 must be anti to the larger ring in order for a transition state for a thermal suprafacial sigmatropic change of order [1,5]<sup>34</sup> to be formed (Fig. 6).



Considering the oxidation of  $\text{COT}^{\cdot-}$  to the tetraene by sulfur dichloride, it is tempting to view the reaction of  $\text{COT}^{\cdot-}$  with dichlorophenylphosphine in analogy with the reaction of  $\text{COT}^{\cdot-}$  with carbon tetrachloride. Thus, the first step would be the reduction of the phosphine to chloride ions and phenylphosphine carbene. The carbene would then add across a double bond of COT to give 45. The absence of any 1,4-addition product 46 or 47 speaks against a nucleophilic mechanism.



## CONCLUSION

The affinity of COT for two electrons and the stability of its dianion illustrate a valid application of the Hückel Rule. The exchange of electrons between the radical anion and the dianion implies a similarity in their structure distinct from that of the neutral molecule. The ease of the further reduction of the radical anion in contrast with the initial reduction of COT is paralleled by the fast nucleophilic reactions of the monoanion in contrast with the slower reaction of the dianion. The organic chemistry of the dianion is varied, including 1,2- and 1,4-nucleophilic additions with rearrangement of products, and reactions in which the dianion is oxidized.

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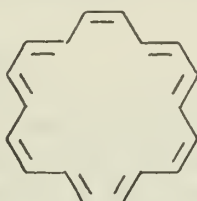
## THE EFFECT OF INTERNAL STERIC INTERACTIONS ON THE COPLANARITY OF [18]ANNULENES

Reported by Sidney Hecht

February 26, 1968

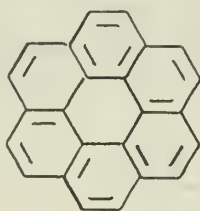
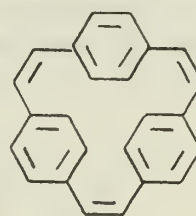
## INTRODUCTION

[18]Annulene (1), first synthesized by Sondheimer,<sup>1-3</sup> is noteworthy in terms of its unusual nmr spectrum which, at room temperature in perdeuteriotetrahydrofuran, consists of one signal at  $\delta$  -2.99 corresponding to the "internal" hydrogens and one signal at  $\delta$  9.28 corresponding to the "external" hydrogens.<sup>4</sup> The observed strong deshielding of the "external" hydrogens relative to "normal" olefinic hydrogens has been interpreted as indicating that the compound has the ability to sustain a diamagnetic ring current about its periphery with an associated secondary magnetic

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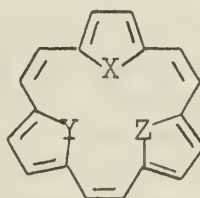
field.<sup>5,6</sup> The fact that smaller annulenes did not exhibit similar nmr spectral characteristics was felt to be due to steric interactions between the "internal" hydrogens which prevented coplanarity of the peripheral ring system.<sup>7</sup>

Coronene (2) is a planar, polycyclic hydrocarbon. The nmr chemical shift of the hydrogens in 2 is  $\delta$  8.85.<sup>8</sup> Thus, while the interior of the ring contains groups which could, in principle, affect the chemical shift of the hydrogens in 2 by electronic interactions with the peripheral ring system, little change is seen from the chemical shift of the "external" hydrogens of [18]annulene.

23

While 1,2,9,10,17,18-dehydro(2.2.2)paracyclophane (3) has essentially the same internal features as compound 2, its "external" hydrogens are considerably more shielded, being found at  $\delta$  6.79. Although 2 is coplanar, 3 cannot even approach coplanarity for steric reasons.<sup>9</sup> Thus, the chemical shift of the "external" hydrogens in [18]annulenes appears to be much more a function of internal steric than of internal electronic effects.

Compounds of type 4, in which X, Y and Z represent heteroatoms of known relative size, provide an excellent opportunity to study the effect of internal steric interaction on coplanarity. Assuming that changes in chemical shift are a function of the changing size of the heteroatoms, and not a function of changing electronic character, the nmr chemical shift of the hydrogens may be employed as a measure of this steric effect.

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The nmr spectra of the annulenes are temperature dependent since, at some temperature, inversions of the type





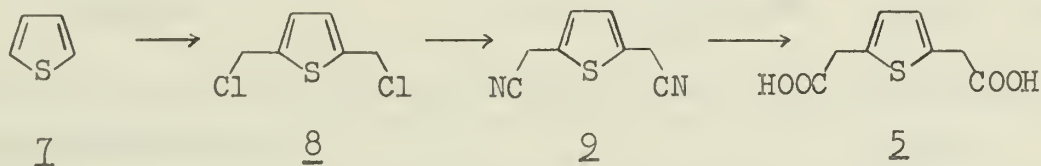


become rapid with respect to the nmr time scale and cause a coalescence of all nmr signals at a position that is the weighted average of the individual signals.<sup>4</sup> This sort of inversion cannot occur in compounds of type 4, since there are no "internal" hydrogens.

Several compounds of type 4 have recently been synthesized. This seminar will deal with the synthetic challenge involved in the preparation of these compounds and with their physical properties.

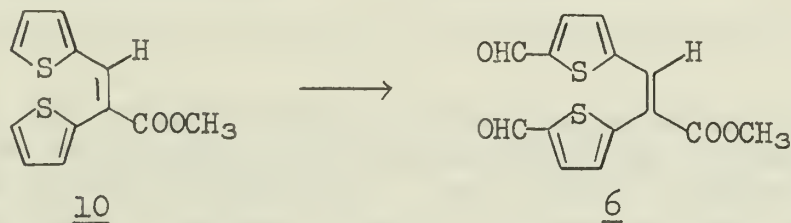
#### SYNTHESIS OF [18]ANNULENE TRISULFIDE

The synthesis of [18]annulene trisulfide<sup>8,10</sup> required the synthesis of two key intermediates, thiophene-2,5-diacetic acid (5) and methyl cis- $\alpha,\beta$ -di-(5-formyl-2-thienyl)acrylate (6). The synthesis of 5 was effected in low yield by the chloromethylation of thiophene and subsequent treatment with sodium cyanide suspended in



dimethylformamide, which gave 2,5-biscyanomethylthiophene (9). Hydrolysis of 9 gave the desired thiophene-2,5-diacetic acid (5).

The synthesis of methyl cis- $\alpha,\beta$ -di-(5-formyl-2-thienyl)acrylate (6) was not as straightforward. It was initially thought that the formylation of methyl cis- $\alpha,\beta$ -di-(2-thienyl)acrylate (10) would give the desired intermediate 6, and attention was directed to synthesis of the ester. The Perkin condensation of benzaldehydes with



phenylacetic acid was known to give a mixture of cis- and trans- $\alpha$ -phenylcinnamic acids, with the trans isomer (the one with the two phenyl groups cis to each other) predominating. The nature of the stereochemical driving force was known,<sup>11</sup> and the reaction appeared applicable to the thiophene case. In fact, when the condensation was attempted, a mixture of the desired cis and trans isomers of methyl  $\alpha,\beta$ -di-(2-thienyl)acrylate was obtained. The isomers were separated by fractional crystallization and the configuration of the products was assigned by various means. For example, it was found that the products esterified at very different rates and a good correlation was made with the rates of esterification of the  $\alpha$ -phenylcinnamic acids<sup>12</sup> (Table I).

This assignment also correlated with the finding that, in compounds of the type  $RCH=CR'-COOR''$ , the olefinic cis hydrogen resonates at lower field than the corresponding olefinic trans hydrogen.<sup>13</sup> Furthermore, as with the  $\alpha$ -phenylcinnamic acids, the compound assigned the cis configuration had a carbonyl absorption at lower frequency in the infrared and absorbed at shorter wavelength in the ultraviolet than did the trans acid<sup>11,14</sup> (Table II).

The synthesis of the necessary methyl cis- $\alpha,\beta$ -di-(2-thienyl)acrylate (10) seemed to offer a route to the key intermediate, methyl cis- $\alpha,\beta$ -di-(5-formyl-2-thienyl)acrylate (6), by direct formylation. An initial attempt at direct



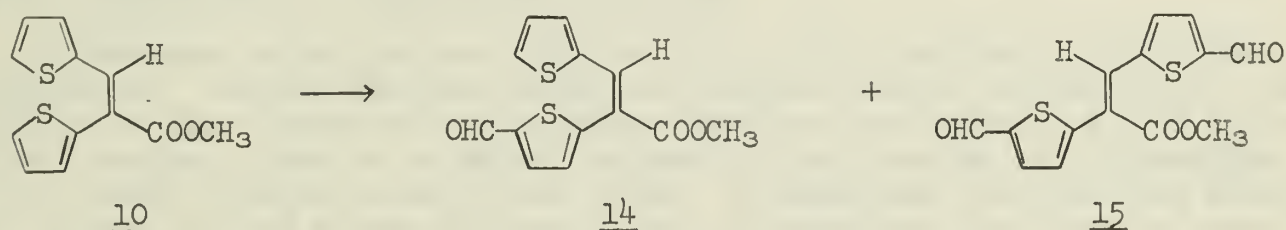
Table I<sup>B</sup> Relative Rates of Esterification

Compound	Relative position of rings about double bond	% ester in one hour
<u>trans</u> - $\alpha$ -phenylcinnamic acid	<u>cis</u>	75.5
<u>cis</u> - $\alpha,\beta$ -di-(2-thienyl)acrylic acid	<u>cis</u>	72.5
<u>cis</u> - $\alpha$ -phenylcinnamic acid	<u>trans</u>	11.9
<u>trans</u> - $\alpha,\beta$ -di-(2-thienyl)acrylic acid	<u>trans</u>	13.0

Table II<sup>B</sup> Spectral Data

Compound	NMR olefinic hydrogen ( $\delta$ )	UV $\lambda_{\max}$ (m $\mu$ )	IR $\nu_{\max}$ (cm <sup>-1</sup> )
<u>trans</u> - $\alpha$ -phenylcinnamic acid		280	1686
<u>cis</u> - $\alpha$ -phenylcinnamic acid		289	1704
<u>cis</u> - $\alpha,\beta$ -di-(2-thienyl)acrylic acid		322	1665
<u>trans</u> - $\alpha,\beta$ -di-(2-thienyl)acrylic acid		340	1700
methyl <u>cis</u> - $\alpha,\beta$ -di-(2-thienyl)acrylate	8.03, 8.04		
methyl <u>trans</u> - $\alpha,\beta$ -di-(2-thienyl)acrylate	7.13, 7.14		

diformylation of 10 by the Vilsmeier-Haak procedure (phosphorous oxychloride and dimethylformamide) gave methyl cis- $\alpha$ -(5-formyl-2-thienyl)- $\beta$ -(2-thienyl)acrylate (14) instead of the desired diformyl compound 6. A more potent formylating agent (N-methylformanilide) was used in another attempt, but this yielded a mixture of 14 and methyl trans- $\alpha,\beta$ -di-(5-formyl-2-thienyl)acrylate (15). Compound 10 was then treated

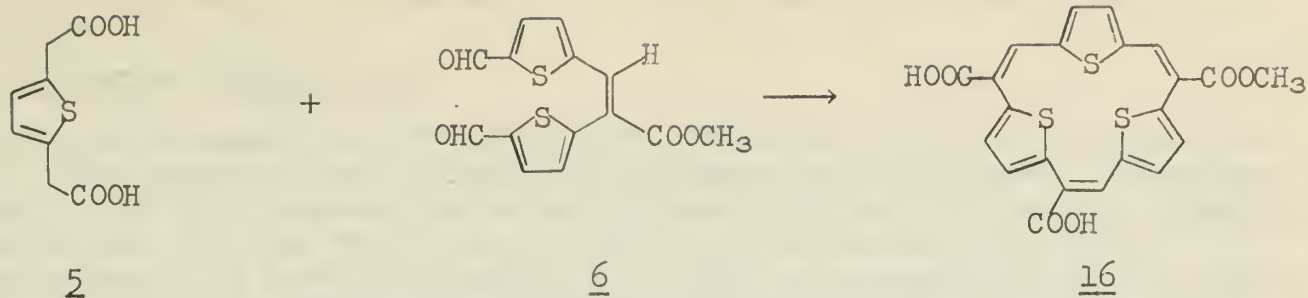


with 1,1-dichloromethyl ethyl ether, phosphorous oxychloride, and stannic chloride, following a formylation procedure developed by Fischer and Schwarz.<sup>15</sup> This procedure gave a mixture of the cis and trans diformyl derivatives, which were separated by chromatography. It was later shown that the trans- $\alpha,\beta$ -di-(5-formyl-2-thienyl)-acrylate could be converted to the cis isomer in high yield by irradiation.

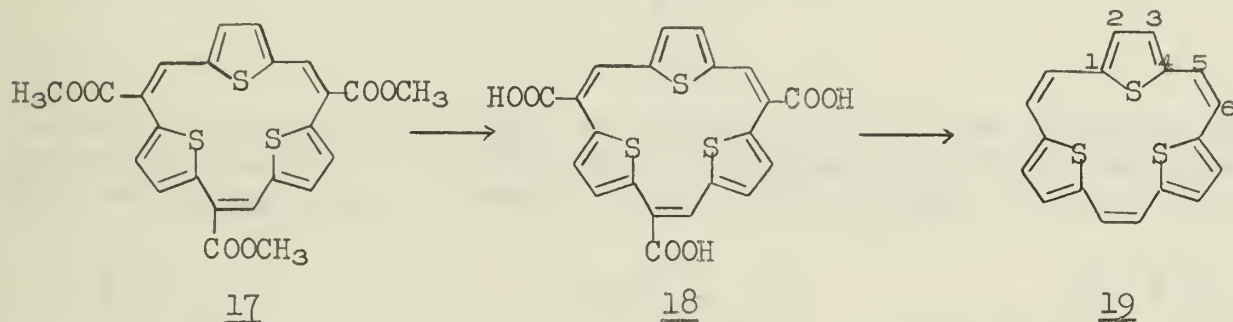
The cyclocondensation of the two key intermediates, 5 and 6, by the Perkin reaction was effected using acetic anhydride and triethylamine. Although the major product was a red polymer, some methyl 5,18-dicarboxy-1,4:7,10:13,16-epithio[18]-annulene-11-carboxylate (16) was isolated. It was found that a better separation could be effected by treating the polymer with methanol-hydrogen chloride and







isolating the resulting methyl 1,4:7,10:13,16-triepthio[18]annulene-5,11,18-tricarboxylate (17). Alkaline hydrolysis of the triester gave 1,4:7,10:13,16-triepthio[18]annulene-5,11,18-tricarboxylic acid (18) in good yield. Decarboxylation of 18



using copper chromite and quinoline gave the desired [18]annulene 1,4:7,10:13,16-trisulfide (19). The structural assignment was confirmed by infrared, ultraviolet, and nmr spectra, and by analysis and molecular weight determination.

#### PREDICTED PROPERTIES OF [18]ANNULENE TRISULFIDE

Coulson, Poole, and Haigh<sup>16-18</sup> carried out Huckel-type MO calculations on [18]-annulene trisulfide to determine the effect on the physical properties of the annulene ring caused by replacement of the "inner" hydrogens by three sulfur atoms. Three sets of parameters were used in the calculations and all led to similar conclusions.

The MO theory predicted that variations would exist in the bond order around the ring, particularly for the C<sub>5</sub>-C<sub>6</sub> (olefinic) bond, which was predicted to have much more double bond character than the other C-C bonds. It also appeared, on the basis of the theory, that there would be a net displacement of  $\pi$ -electrons into the peripheral ring system from the heteroatoms, but that this effect would be small. Models suggested that the molecule could not be coplanar due to internal steric interactions.<sup>8</sup>

#### PHYSICAL PROPERTIES OF [18]ANNULENE TRISULFIDE

[18]Annulene trisulfide was a yellow solid, which sublimed at 70° without decomposition. Its nmr spectrum showed two signals (carbon tetrachloride); one at  $\delta$  6.68 due to the protons on the thiophene rings and the other at  $\delta$  6.73 due to the olefinic protons. This is in marked contrast to the spectrum of [18]annulene which has its "outer" protons at much lower field. A comparison with the data obtained from coronene (2) and triene 3 suggests that [18]annulene trisulfide is rather like three thiophene units connected by three olefinic double bonds.

The ultraviolet spectra support this view. A comparison of the spectra of 2-vinyl and substituted 2-vinyl thiophenes with those of the corresponding benzene derivatives suggests that the thiophenes should generally be about 30 m $\mu$  to longer wavelength. Since the nmr spectrum of triene 3 indicated that it might be a good model for [18]annulene trisulfide, it is interesting to note that the ultraviolet spectra of the two are very similar in shape, but that the  $\lambda_{\text{max}}$  for [18]annulene trisulfide are about 30 m $\mu$  to longer wavelength. This correlates well with the postulate that triene 3 is a good model for [18]annulene trisulfide and that the latter must, therefore, also deviate from planarity. By way of comparison, the



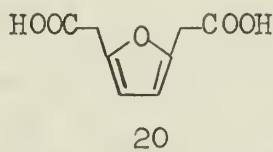


ultraviolet spectrum of [18]annulene trisulfide is quite different from that of [18]annulene.

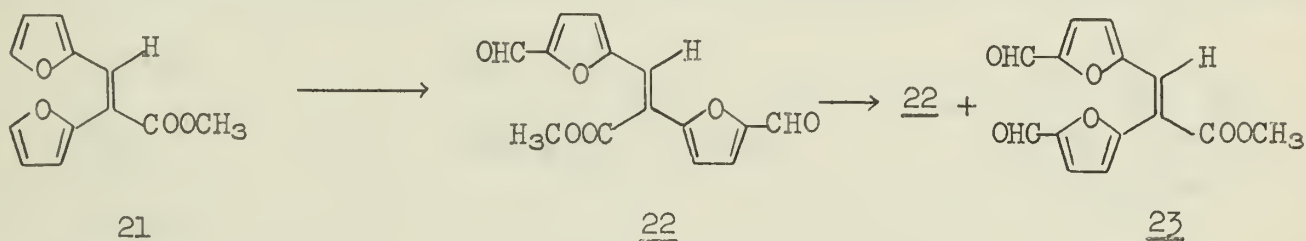
# OTHER [18]ANNULENE HETEROCYCLES

While models suggested that [18]annulene trisulfide would be a non-coplanar molecule, they suggested that [18]annulene trioxide would be planar.<sup>7</sup> Therefore, the synthesis of this compound was of considerable interest, and it was ultimately achieved in much the same way as the synthesis of [18]annulene trisulfide.<sup>19,20</sup>

The synthesis of furan-2,5-diacetic acid (20) was accomplished by the method of Novitskii, Yun'ev and Zhinganeva<sup>21</sup> which involved a sequence analogous to that used to make the thiophene diacid 5. The other key intermediate, methyl cis- $\alpha,\beta$ -di-

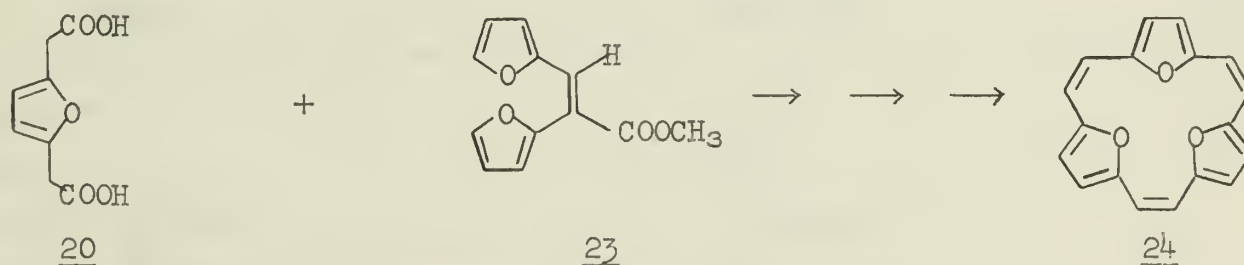


(5-formyl-2-furyl)acrylate (23), was synthesized as in the thiophene case, except that formylation of the intermediate methyl cis- $\alpha,\beta$ -di-(2-furyl)acrylate (21) would yield only trans- $\alpha,\beta$ -di-(5-formyl-2-furyl)acrylate (22). It was found, however, that



irradiation of 22 would yield an equal mixture of cis- and trans-di-formyl derivatives, and that these could then be separated. The assignment of configuration was made as before.

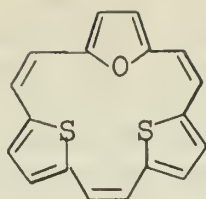
Condensation of the two key intermediates gave the desired ring system, and [18]annulene trioxide (24) was obtained as deep red prisms from the initial product by alkaline hydrolysis of the ester linkage and decarboxylation of the tricarboxylic acid using copper chromite and quinoline. The nmr spectrum showed two signals at low field ( $\delta$  8.68, 8.66), comparable in position to those of [18]annulene and coronene (2), and its ultraviolet spectrum was somewhat similar to that of [18]annulene. These low field nmr absorptions and the ultraviolet spectrum indicated that the [18]annulene trioxide molecule should be considered quite different from three furans connected by ordinary olefinic bonds, and certainly quite different from the non-coplanar [18]annulene trisulfide.



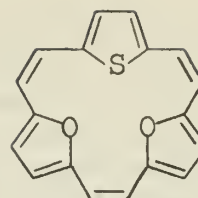
The apparent coplanar character of [18]annulene trioxide in contrast to the non-coplanar situation in [18]annulene trisulfide raised the question of the nature of the physical properties of the intermediate cases, [18]annulene 1,4-oxide-7,10:13,16-disulfide (25) and [18]annulene 1,4:7,10-dioxide-13,16-sulfide (26). These compounds were prepared by the same type of cyclocondensation used to make [18]annulene trisulfide.

[18]Annulene oxide disulfide (25) was isolated<sup>19,22</sup> as yellow needles and its nmr spectrum had a variety of signals from  $\delta$  6.42 to  $\delta$  7.10. The wide spread of these signals and the fact that they are all quite shielded relative to the signals





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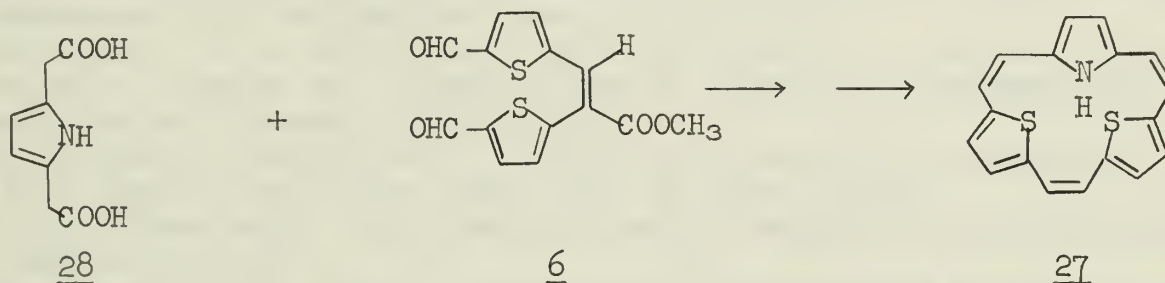


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in [18]annulene trioxide suggested that the molecule was not a coplanar species. Moreover, the ultraviolet spectrum, which was unlike that of [18]annulene, was consistent with this view.

The isolation of [18]annulene dioxide sulfide (26)<sup>23,24</sup> and the subsequent determination of its nmr spectrum, which consisted of a variety of signals in the range  $\delta$  8.29-9.00, suggested that a coplanar species could not be excluded. This absorption at low field in the nmr was quite different from the absorption of [18]-annulene trisulfide and [18]annulene oxide disulfide, and the ultraviolet absorption spectrum was similar to those of [18]annulene and [18]annulene trioxide.

One [18]annulene heterocycle that contains an imino bridge is known: 1,4-epimino[18]annulene 7,10:13,16-disulfide (27). Its synthesis was effected by analogy with earlier syntheses through the cyclocondensation of pyrrole-2,5-diacetic



acid (28) and methyl *cis*- $\alpha,\beta$ -di-(5-formyl-2-thienyl)acrylate (6).<sup>25,26</sup> Compound 27 was obtained in the form of yellow needles and its nmr spectrum showed a series of signals from  $\delta$  6.40 to  $\delta$  7.00 corresponding to the "external" hydrogens. These values are quite similar to those obtained for [18]annulene oxide disulfide, suggesting that 27 should also be regarded as consisting of three heterocyclic rings connected by three olefinic double bonds. The nmr spectra of a number of 18  $\pi$ -electron systems are summarized in Table III.

Table III<sup>24</sup> NMR  $\delta$  Values of Some 18  $\pi$ -Electron Systems (25°)

Compound	"External" Hydrogens	"Internal" Hydrogens
[18]Annulene	9.28	-2.99
Coronene	8.85	
[18]Annulene trioxide	8.66,8.68	
[18]Annulene dioxide sulfide	8.29-9.00	
[18]Annulene oxide disulfide	6.42-7.10	
Epimino[18]annulene disulfide	6.40-7.00	8.23
[18]Annulene trisulfide	6.68,6.73	

For the series of five [18]annulene heterocycles, [18]annulene trisulfide represents one extreme; the chemical shift of its hydrogens approaches that of the







non-coplanar triene 3; at the other end of the series, the hydrogens of [18]-annulene trioxide have chemical shift positions approaching that of the planar compound coronene (2). Furthermore, among these heterocycles, there is a relationship between the chemical shift of the "external" hydrogens and the size of the heteroatoms. Since we know that the chemical shift is a function of the coplanarity of the peripheral ring system, the change in the chemical shift with the various heteroatoms is best explained by the change in coplanarity that these heteroatoms effect in the [18]annulene ring system by their steric interactions.

## CONCLUSION

It has been found that the nmr chemical shift value of the "external" hydrogens is a reasonable gauge of the coplanarity of a given [18]annulene ring system and that this nmr value is essentially insensitive to internal electronic effects. It was noted that for [18]annulene heterocycles a relationship exists between the degree of steric interaction and the chemical shift. It was suggested that this change in chemical shift may be due to changes in coplanarity caused by variations in the degree of steric interaction.

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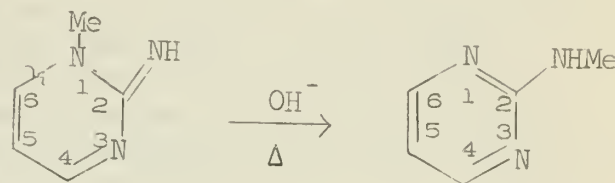
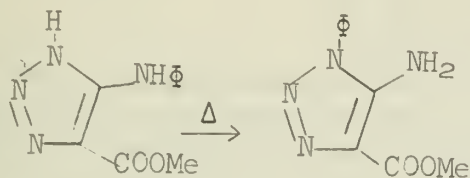


## THE DIMROTH AND RELATED REARRANGEMENTS

Reported by Stephen R. Byrn

March 18, 1968

In 1927 Dimroth discovered a rearrangement in the triazole series,<sup>1</sup> and recently Brown has studied a formally analogous rearrangement in the pyrimidine series.<sup>2</sup>



These reactions are examples of the Dimroth rearrangement, which appears to involve alkyl or aryl migration. Mechanistic studies indicate that the Dimroth rearrangement, of the two compounds shown above, involves a ring-opened intermediate, formed by cleavage of the designated bond, and closure to the rearranged product.

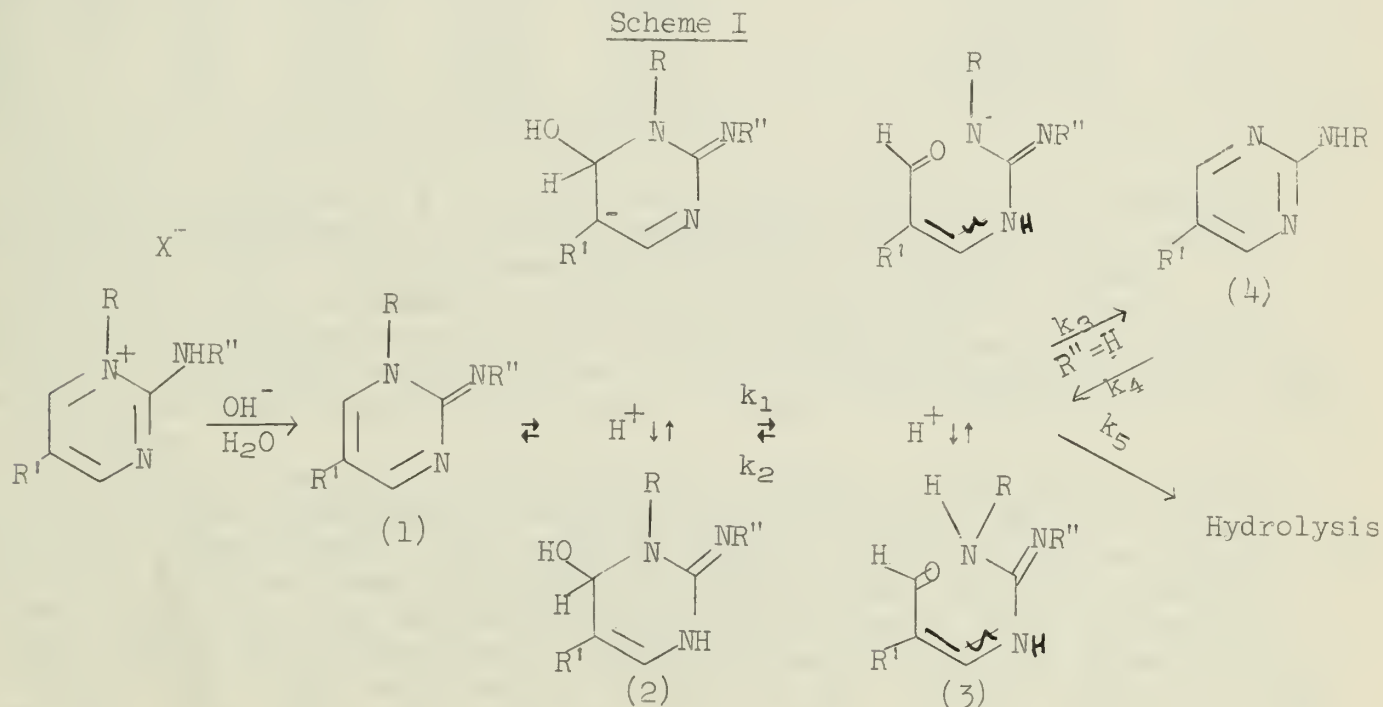
In this seminar, this general mechanism will be used to explain several related rearrangements and, in conclusion, it will be suggested that this mechanism is useful for the planning of syntheses and the directing of further mechanistic work.

## MECHANISTIC INVESTIGATIONS IN THE PYRIMIDINE SERIES

The proposed mechanism for the Dimroth rearrangement in the pyrimidine series is based on labeling studies, kinetic studies, and characterization of some of the intermediates.

The rearrangement is usually carried out by placing the pyrimidine-hydrohalide salt in aqueous base. Labeling studies using <sup>15</sup>N show that all the label on the exocyclic N is incorporated into the ring.<sup>2,3</sup> Thus a mechanism involving methyl migration is eliminated.

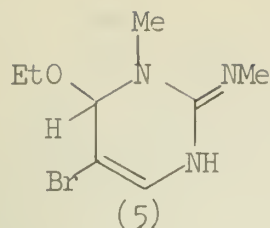
On the basis of kinetic studies and the isolation of intermediates Perrin suggested the mechanism shown in scheme I.<sup>4</sup>



Bisulphite ion and ethanol formed 1:1 adducts with (1). The equilibrium constant for the formation of the bisulphite adduct was calculated on the basis of ultra-violet measurements. Both the 4- and 6-methyliminopyrimidines had smaller equilibrium constants than their unmethylated analogues; which suggested that these two positions may be the site of addition. NMR spectra of ethanol solutions (pH 9-12) of (1) (R = Me, R' = Br, R'' = Me) indicated that (5) was formed, but the 4-adduct cannot be rigorously ruled out.







Fast reaction techniques were used to show that the formation of (2) was first-order and was too fast to be the rate-determining step in the formation of (4) from (1). Addition of acid to this solution regenerated the cation of (1); therefore, the formation of (2) is probably reversible. It was also shown that in dry solvents (1) was not converted to (4); thus, the addition of nucleophiles to (1) appears to be a necessary step in the conversion of (1) to (4).

For the compounds listed in table I, no reaction was observed when the corresponding rearranged product (4) was added to base, indicating that  $k_4 \sim 0$ . Only traces of hydrolysis products were found when the rearrangement was carried out, thus,  $k_3 > k_5$  and  $k_2 > k_5$ . Furthermore, equations for evaluating  $k_1$ ,  $k_2$ , and  $k_3$

in the system  $(2) \xrightleftharpoons[k_2]{k_1} (3) \xrightarrow{k_3} (4)$  were derived assuming  $k_1 > k_3$ . Ultraviolet

measurement of the required rates of disappearance enabled the calculation of  $k_1$ ,  $k_2$ , and  $k_3$  (cf. Table I). All of these reactions had the same  $E_a$  within experimental error (cf. Table II). The  $\Delta S^\ddagger$  was less than 10 cal/deg for all of these reactions. Changing the ionic strength from 0.05 to 1.0 had little effect on these rates; that is, there was no salt effect. Addition of base had no effect on  $k_1$ ,  $k_2$ , and  $k_3$  for (1) ( $R = \text{Me}$ ,  $R' = \text{I}$ ,  $R'' = \text{H}$ ); the reaction was not base catalyzed. If  $k_3 > k_1$  (2) appeared to go directly to (4) as was the case with (2) ( $R = \text{Me}$ ,  $R' = R'' = \text{H}$ ).

Table I

Compound (1)			$k_1$	$k_2$	$k_3$
R	R'	R''	(min <sup>-1</sup> )	(min <sup>-1</sup> )	(min <sup>-1</sup> )
Me	Cl	H	0.29	0.07	0.02
Me	Br	H	0.29	0.08	0.02
Et	Br	H	0.26	0.04	0.02
Me	Br	Me	0.06	0.03	----
Me	I	H	0.21	0.08	0.03

Table II

Reaction	$E_a$ kcal/mole
$(2) \xrightarrow{k_1} (3)$	$18.5 \pm 0.5$
$(3) \xrightarrow{k_2} (1)$	$20.5 \pm 1.5$
$(3) \xrightarrow{k_3} (4)$	$22.5 \pm 0.5$

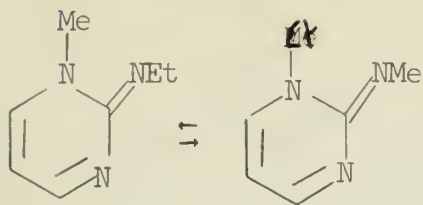
The effect of changing  $R'$  or  $R$  in compound (1) on the rate of the overall reaction was investigated.<sup>5,6</sup> Electron withdrawing groups in either position accelerated the rate. Electron donating groups had the opposite effect.

Unfortunately few mechanistic conclusions can be drawn from these results since it is not clear which of the rates the substituent affects. A study of the effect of changing  $X$  in (1) ( $R = \text{Me}$ ,  $R' = \text{H}$ ,  $R'' = p\text{-X-phenyl}$ ) on  $k_1$ ,  $k_2$ , and  $k_3$  would do much to illustrate the electronic nature of the transition state of these reactions.

A considerable amount of chemical evidence supporting the kinetic analysis presented above has accumulated. Compound (3) ( $R = \text{Me}$ ,  $R' = \text{CN}$ ,  $R'' = \text{H}$ ) was isolated and characterized.<sup>7</sup> This compound gave the correct elemental analysis and its infrared spectrum showed absorptions at 2200 cm<sup>-1</sup> and 1650 cm<sup>-1</sup>. No nmr spectrum was reported. In base this compound rearranged to the corresponding (2) and (4) and to an abnormal product involving ring closure with CN rather than CHO. Several other (3)'s were trapped as their oximes. Further support for the intermediacy of (3) came from the nmr of (1) ( $R = \text{Me}$ ,  $R' = \text{H}$ ,  $R'' = \text{Me}$ ) in 0.05 M NaOD. The nmr of this solution showed starting material and a species with equivalent methyl groups which was probably the corresponding (3). The reaction shown below reached equilibrium when either pure isomer was added to base. Thus,  $(2) \xrightleftharpoons[k_2]{k_1} (3)$  is reversible.<sup>8</sup>



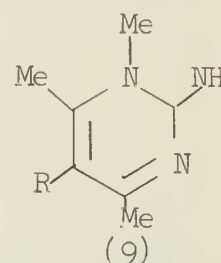
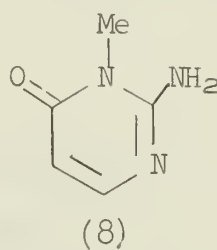
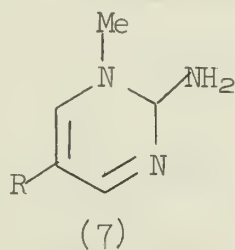
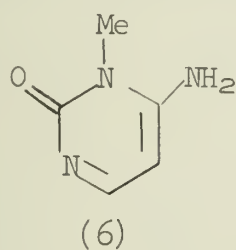




In summary, the kinetic and chemical evidence support mechanisms of the general type  $A \rightleftharpoons B \rightleftharpoons C \rightleftharpoons D$ , where A is starting material, B is the 1:1 adduct of nucleophiles, C is the ring-opened intermediate, and D is the rearranged product.

Under certain conditions the hydrolysis of (1) and similar compounds was observed. For example, the addition of (1) ( $R = \text{Me}$ ,  $R' = R'' = \text{H}$ ) to aqueous base (ph 9-12) yielded the corresponding rearranged product (4) and 2-hydroxypyrimidine.<sup>9</sup> The rearranged product was stable under these conditions. It was suggested that in this case  $k_2 \sim k_3 \sim k_5$  and  $k_4 \sim 0$ ; but, direct hydrolysis of (1) cannot be rigorously ruled out.

Compounds (6),<sup>10</sup> (7),<sup>11</sup> and (8)<sup>12</sup> hydrolyze rather than rearrange when placed in base. The hydrolysis of (6) and (8) can be explained by a scheme analogous to scheme I with  $k_2 \sim k_3 \sim k_5$ .

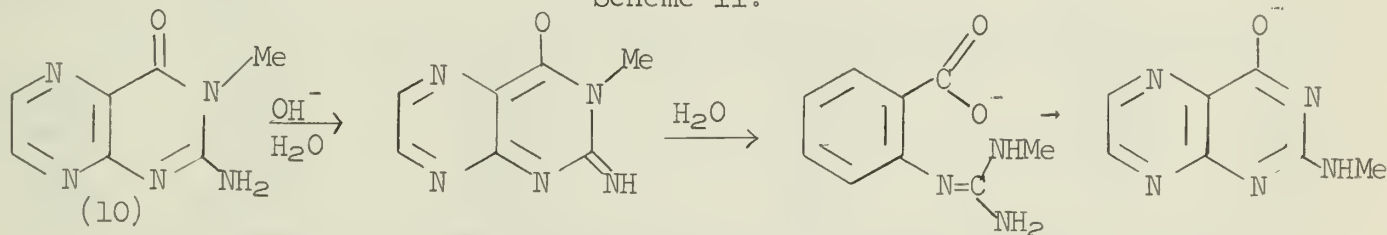


Compounds (1) ( $R = \text{Me}$ ,  $R' = R'' = \text{H}$ ) and (9) rearrange under the same conditions that (7) hydrolyzes. These results can be explained by a scheme analogous to scheme I as follows: for (7)  $k_2 \sim k_3 \sim k_5$ ; however, for (1) ( $R = \text{Me}$ ,  $R' = R'' = \text{H}$ ) and (9),  $k_2 > k_5$  and  $k_3 > k_5$ .

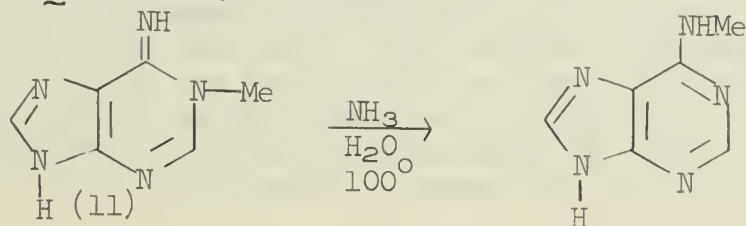
Several other reactions, which are similar to the Dimroth rearrangement in the pyrimidine series, were carried out in acid or base. Some of these were reported without experiments necessary to illustrate the mechanism. Mechanisms of the general type  $A \rightleftharpoons B \rightleftharpoons C \rightleftharpoons D$  can be used to explain these reactions and enable one to unify the data.

The rearrangement of the pteridine derivative (10) was found to be base catalyzed. Kinetic studies indicated that the reaction involves two consecutive reactions. Brown suggested the mechanism shown in scheme II. A reaction sequence of the general type found in the pyrimidine series with the reverse reactions much slower than the forward reactions and involving base catalysis can explain the data as well as scheme II.

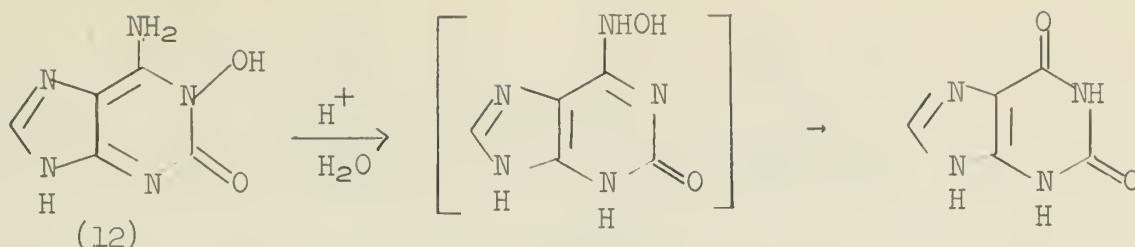
Scheme II.<sup>13</sup>



In the purine series the rearrangements of (11)<sup>14</sup> and (12)<sup>15</sup> are observed. It seems possible that the rearrangement of (11) takes place with the general mechanism  $A \rightleftharpoons B \rightleftharpoons C \rightleftharpoons D$ . The hydrolysis of (12) could involve Dimroth rearrangement (with the same general mechanism) to the hydroxylamine and hydrolysis of this compound as shown. It is also possible that the path of this reaction is similar to the path of the hydrolysis of (1) ( $R = \text{Me}$ ,  $R' = R'' = \text{H}$ ).





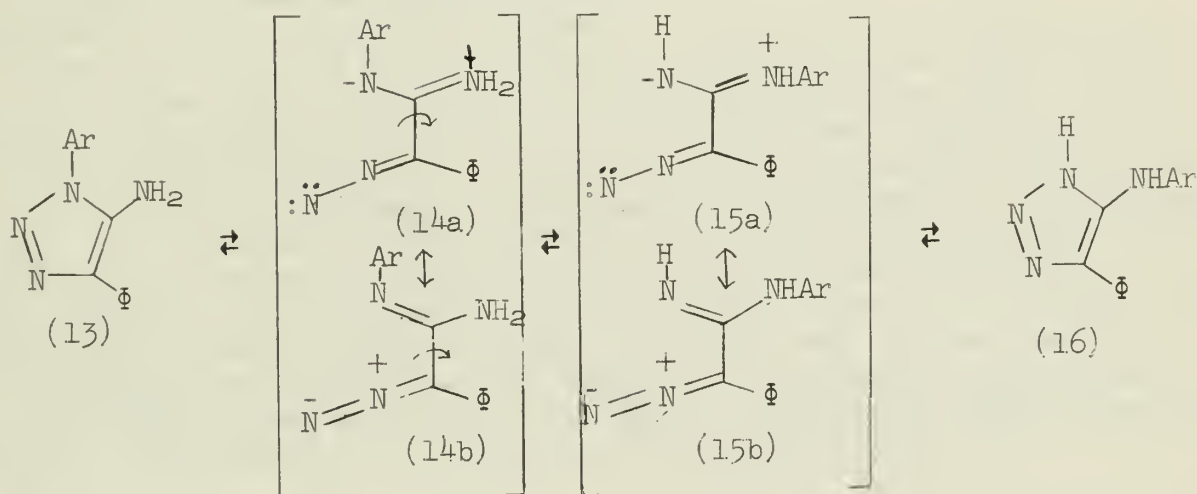


# MECHANISTIC INVESTIGATIONS IN TRIAZOLE SERIES

The Dimroth rearrangement of triazoles is usually carried out in a solvent such as ethylene glycol, and an equilibrium is often reached.

The proposed mechanism for the rearrangement in the triazole series is shown in scheme III and is based on a study of the effect of substituents on the rate of

Scheme III



the forward ( $k_f$ ) and reverse ( $k_r$ ) reactions. Table III summarizes the  $k_f$ ,  $k_r$ ,  $E_a$ ,  $\Delta S^\ddagger$ , and  $K_{eq}$  obtained for different (13)'s in ethylene glycol.<sup>16</sup>

Table III\*

Ar in (13)	$k_f \times 10^2$ ( $\text{min}^{-1}$ )	$E_a$ (kcal/mole) (for. rxn.)	$\Delta S^\ddagger$ (cal/deg) (for. rxn.)	$k_r \times 10^2$ ( $\text{min}^{-1}$ )	$K_{eq}$
Ph	1.25	25.22	-14.0	0.26	4.8
p-MePh	0.71	28.07	-7.9	0.26	2.7
p-MeOPh	0.52	30.15	-3.5	0.29	1.8
m-ClPh	2.88	25.13	-12.3	0.15	19.1
p-NO <sub>2</sub> Ph	12.30	21.50	-18.5	----	----

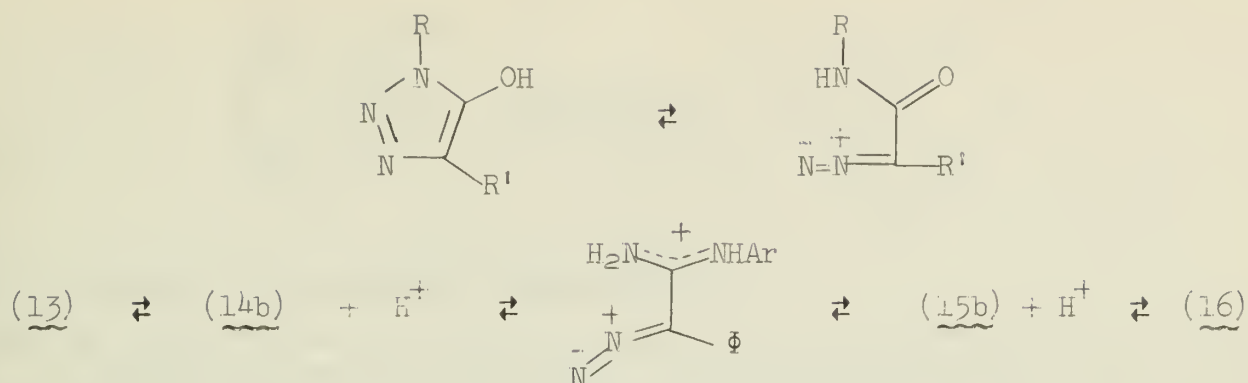
\*All rates were measured at 133°C.

Electron withdrawing substituents accelerate the forward reaction ( $\rho_f = 0.9$ ) and have little effect on the reverse reaction ( $\rho_r = -0.03$ ). The  $E_a$  for the reverse reaction ranges from 30-35 kcal/mole. A discussion of the meaning of these substituent effects and the mechanism presented in scheme IV will be presented shortly.

Brown studied the rearrangement of (13) in acidic ethanol at 80°C. He found that the rate  $\propto [\text{H}^+][\text{triazole}]$  when  $[\text{H}^+] < 10^{-4}$  and rate  $\propto [\text{triazole}]$  when  $[\text{H}^+] > 10^{-4}$ . The effect of substituents on the benzene ring on the rates of the forward and reverse reactions was similar to that reported in table III.<sup>17</sup> On the basis of this evidence and the known ring-chain tautomerism<sup>18</sup> he suggested a mechanism involving protonation of the ring-opened intermediate (e.g., 14b).



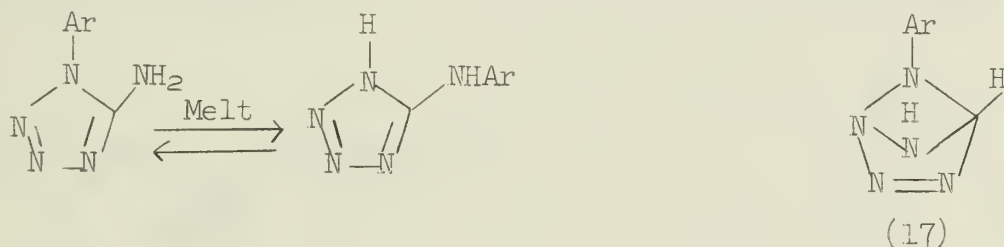




Originally, Brown proposed (14b) and (15b) as intermediates in the triazole rearrangement; whereas, Lieber proposed (14a) and (15a) as the only intermediates. Since (14a) and (14b) as well as (15a) and (15b) are resonance structures, these two workers proposed the same mechanism.

An explanation of the substituent effects (cf. Table III) is based on the idea that the aryl group sees a different electronic distribution approaching the transition state of the rate determining step from (13) than from (16). A rate determining step involving N-N heterolytic fission can explain these substituent effects. However, two other possible rate determining steps cannot be rigorously ruled out: (1) the rotation of the C-C bond in (14)  $\rightleftharpoons$  (15); and (2) the tautomerism in (14)  $\rightleftharpoons$  (15). It is unlikely that tautomerism is the rate determining step, because proton transfers between two heteroatoms are usually extremely fast. Deuterium isotope effect studies would help answer this question. There is no obvious reason why rotation of the C-C bond should be ruled out as the rate determining step.

Lieber suggested that the thermal rearrangement of tetrazoles took place by a mechanism analogous to that presented in scheme III, since substituents had an analogous effect on the rate of the forward and reverse reactions.<sup>19</sup>

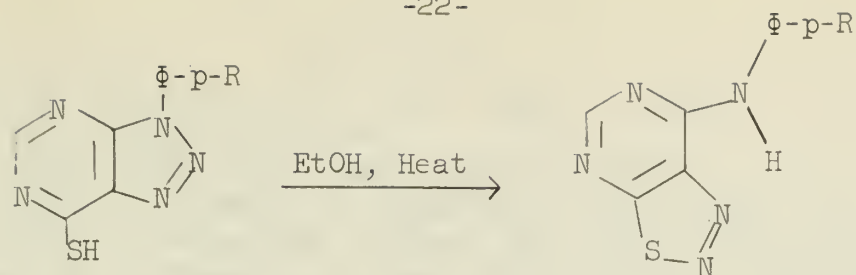


Garbrecht, however, suggested that the intermediate in the tetrazole rearrangement may be (17).<sup>20</sup> Lieber argued that the strain in (17) would be very large and ruled out a mechanism in the triazole or tetrazole series involving this kind of intermediate. The possibility of a mechanism involving (17) should be considered until it is ruled out experimentally. The rearrangements in the triazole and tetrazole series could also proceed by homolytic scission of the N-N bond. None of these workers attempted to trap or detect radicals.

It seems likely that the Dimroth rearrangement of triazoles and tetrazoles proceeds by a mechanism of the general type A  $\rightleftharpoons$  C  $\rightleftharpoons$  D, where A is starting material, C is the ring-opened intermediate, and D is the product. This general mechanism is similar to that for the Dimroth rearrangement in the pyrimidine series but does not involve the 1:1 adduct of nucleophiles, B.

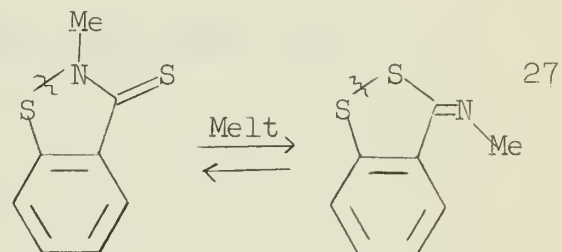
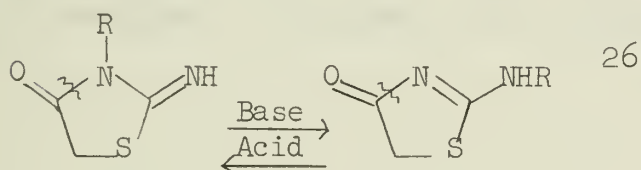
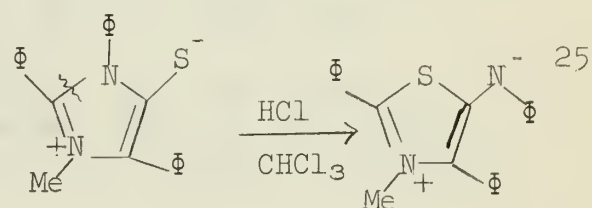
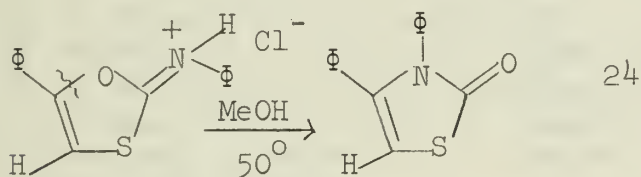
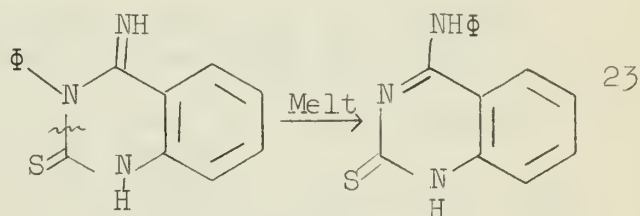
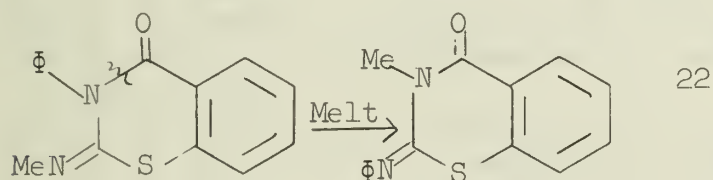
At least one recently observed reaction could go by a similar path. Brown and Paddon-Row studied the reaction shown below.<sup>21</sup> They found that electron withdrawing R groups accelerated the forward reaction ( $\rho = 1.5$ ) and slightly decelerated the reverse reaction. The equilibrium constant was less than 0.10 in all cases. Brown suggested that these results were consistent with a rate determining N-N heterolytic fission.





## REACTIONS RELATED TO THE DIMROTH REARRANGEMENT

The six reactions shown below have been recently reported without mechanistic study. An examination of the structures of the starting materials and the products suggest that these reactions are similar to the Dimroth rearrangements in the pyrimidine and triazole series. It is likely that these reactions take place by one of the two general mechanisms  $A \rightleftharpoons B \rightleftharpoons C \rightleftharpoons D$  or  $A \rightleftharpoons C \rightleftharpoons D$ . These reactions probably indicate the scope of the Dimroth rearrangement in heterocyclic systems, and suggest the synthetic utility of this rearrangement.



## CONCLUSION

The Dimroth rearrangement involves apparent alkyl or aryl migration. Mechanistic studies discussed above indicate that, in these cases, the Dimroth rearrangement involves a ring-opened intermediate which can close to form products or starting material. The ring-opened intermediate in the thermal Dimroth rearrangement (triazole series) is probably formed by heterolytic cleavage of a ring bond. In other cases the heterolytic cleavage of a ring bond is probably preceded by addition of a nucleophile (pyrimidine series). These reactions involve complicated kinetic schemes which are either of the type  $A \rightleftharpoons B \rightleftharpoons C \rightleftharpoons D$  or  $A \rightleftharpoons C \rightleftharpoons D$ , where B is the adduct of a nucleophile and C is a ring-opened intermediate. Slight variation of a rate constant (or constants) by structural changes or changes in conditions may alter the course of the reaction.

It is likely that reactions related to the Dimroth rearrangement proceed by one of these general mechanisms. The mechanistic work presented in this seminar, although sparse, appears to provide one with a scheme which can explain a large number of reactions in heterocyclic systems. This general mechanism may also be useful in planning syntheses and directing further mechanistic work.





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## THE CYCLOPROPYL CATION

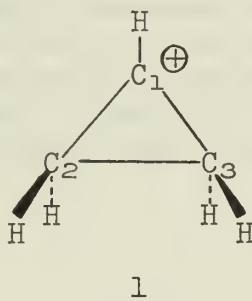
Reported by A. Harry Andrisc

March 21, 1968

## INTRODUCTION

Extensive and conclusive evidence is presented in the chemical literature for the existence of carbonium ions both as stable, isolable salts and as short-lived reaction intermediates.<sup>1</sup> The behavior of cycloalkyl cations becomes more dissimilar from that exhibited by the acyclic analogues as the ring size decreases. The lowest member in the homologous series of cycloalkyl cations, the cyclopropyl cation, is of particular interest both because angle strain is maximized and because of the unique hybridization. Cyclopropyl derivatives have carbon-carbon bonds containing considerably more p-character and carbon-hydrogen bonds with more s-character than ordinary  $sp^3$ -hybridized bonds.<sup>2</sup>

It is the intention of this seminar to review the evidence for the existence of the cyclopropyl cation (1) as a reaction intermediate and to investigate other proposed mechanistic rationales for carbonium ion-type reactions of cyclopropyl derivatives. Solvolysis of cyclopropyl tosylates<sup>3</sup> and other aspects of the cyclopropyl cation problem have been reviewed.<sup>4-6</sup> In this discussion the classical cyclopropyl cation (1) will be considered to possess the following restrictions: a full  $C_2-C_3$   $\sigma$ -bond and  $C_{2v}$  symmetry. Although syntheses of compounds necessary for the kinetic and product studies discussed below have been challenging and of interest



in their own right, they will not be elaborated here since reviews are available.<sup>3,7</sup>

## PRODUCTS, RATES, AND SUBSTITUENT EFFECTS IN SOLVOLYSIS OF CYCLOPROPYL DERIVATIVES

Attempts to generate ion 1 have generally led to allyl rather than cyclopropyl products. Kishner<sup>8a</sup> and Lipp<sup>8b</sup> independently isolated allyl alcohol as the sole product from the nitrous acid deamination of cyclopropylamine. When Corey and Atkinson repeated this experiment with cyclopropylamine-1-d, nmr analysis showed the isolated allyl alcohol to contain essentially all deuterium at  $C_2$ .<sup>9</sup> This result suggested exclusive  $C_2-C_3$  bond cleavage was operative and that 3-diazopropanol and the corresponding carbene were not deamination intermediates. Similarly, acetolysis of cyclopropyl tosylate gave allyl acetate in quantitative yield.<sup>10</sup> Ring-opening of cation 1 has been postulated for the observed facile addition of acids to cyclopropanone<sup>11</sup> and cyclopropenes.<sup>12a</sup> The classical cation 1, if ever fully formed, must have a considerable inherent driving force for rearrangement to the more stable allyl cation. This propensity for rearrangement has not been observed for the cyclopropyl anion<sup>12b</sup> or radical.<sup>12c</sup>

Roberts and Chambers observed that cyclopropyl tosylate underwent solvolysis in anhydrous acetic acid  $10^5$  times slower than cyclohexyl tosylate.<sup>10,13</sup> Although they did not invoke ion 1 as an intermediate, they did note that the characteristic stabilization of the allyl cation was not reflected in the transition state, thus making it unlikely that the allyl cation was formed directly in the rate-determining step. Brown has postulated inordinate internal angle strain ("I-strain") in going to the assumed trigonal transition state (1) to explain this extraordinary inertness,<sup>14</sup> while Cromwell and Graff suggested added ground state stabilization by  $\pi$ -overlap between substituent p-orbitals and the bent bonds of the Coulson-Moffitt model.<sup>15</sup> Analogy with vinyl and phenyl groups has also been adduced as a factor pertinent to the issue.<sup>10,16</sup>

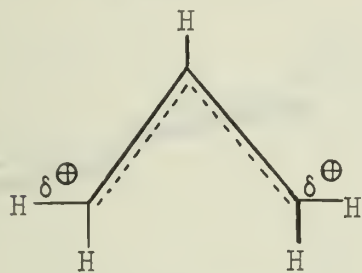
Schleyer and Nicholas have pointed out that although the internal bridge angle



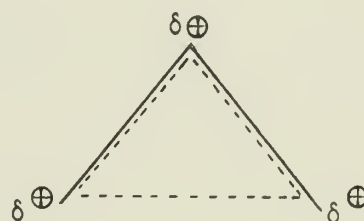


in 7-norbornyl tosylate is  $98.3^\circ$  and the internal angle in cyclopropyl tosylate is  $60^\circ$ , the latter solvolyzes some  $10^2$  times faster than the former.<sup>17</sup> By comparison with 2-adamantane derivatives, the slowness in the 7-norbornyl system was attributed to angle strain alone. Applequist and Landgrebe have calculated the difference in strain energy between ion 1 and a cyclopentyl cation from the difference in heats of hydrogenation of 2-methyl-1-methylenecyclopropane and methylenecyclopentane.<sup>18,19</sup> Comparison of solvolytic rates and assuming only the same rate ratio for the tosylates and chlorides, cyclopropyl chloride was calculated to show a rate enhancement of some  $10^3$  over that predicted for solvolysis by way of 1.<sup>19</sup> Employment of the well-known Foote<sup>20</sup> and Schleyer<sup>21</sup> correlations of carbonyl stretching frequency with tosylate acetolysis rate predicts considerable anchimeric assistance in the solvolysis of cyclopropyl tosylate. Foote<sup>20</sup> calculated a rate enhancement of  $10^5$ , however, this correlation is based on rather poor models for extrapolation to small-ring systems. The more elaborate treatment by Schleyer,<sup>21</sup> taking into account torsional and non-bonded interaction strains, produced the more realistic acceleration of  $10^2$ . These results suggested that considerable anchimeric assistance is operative in the solvolysis of cyclopropyl tosylate and that the reaction path by-passes ion 1 on the way to a transition state already stabilized by some allylic resonance.<sup>4</sup>

If solvolysis does proceed through ion 1, then the presence of assistance is difficult to explain. An examination of substituent effects on solvolysis rates is necessary for an evaluation of charge delocalization in the transition state and to determine whether or not the reaction is concerted. For localized cations  $\alpha$ -methyl and  $\alpha$ -phenyl substituents have large rate-accelerating effects (ca.  $10^5$  and  $10^{10}$ - $10^{12}$ , respectively), while  $\beta$ -methyl substitution has a negligible effect (ca. 1-3). The converse holds for delocalized transition states, such as 2 or 3; for example, in the formolysis of allyl chloride methyl substitution gave the following accelerations in rate: 1-methyl,  $5.67 \times 10^3$ ; 2-methyl, 0.5; 3-methyl,  $3.55 \times 10^3$ .<sup>22</sup>






2











3

Substituent effects on solvolysis rates of cyclopropyl derivatives are compiled in Table I where rates are relative to the unsubstituted derivative under the same reaction conditions. Since these rate data clearly demonstrate considerable charge accumulation at C<sub>2</sub> and C<sub>3</sub> and withdrawal from C<sub>1</sub> in the transition state, Schleyer proposed the non-classical cation 3,<sup>4,23</sup> it is to be noted, however, that the nature of the C<sub>2</sub>-C<sub>3</sub> bonding interaction and the positions of protons were not specified.

Table I. Relative Solvolytic Rate Constants  
for Substituted Cyclopropyl Derivatives

Compound	<u>k<sub>rel</sub></u>	Reference
	40	24
	180	4
	$10^5$	25



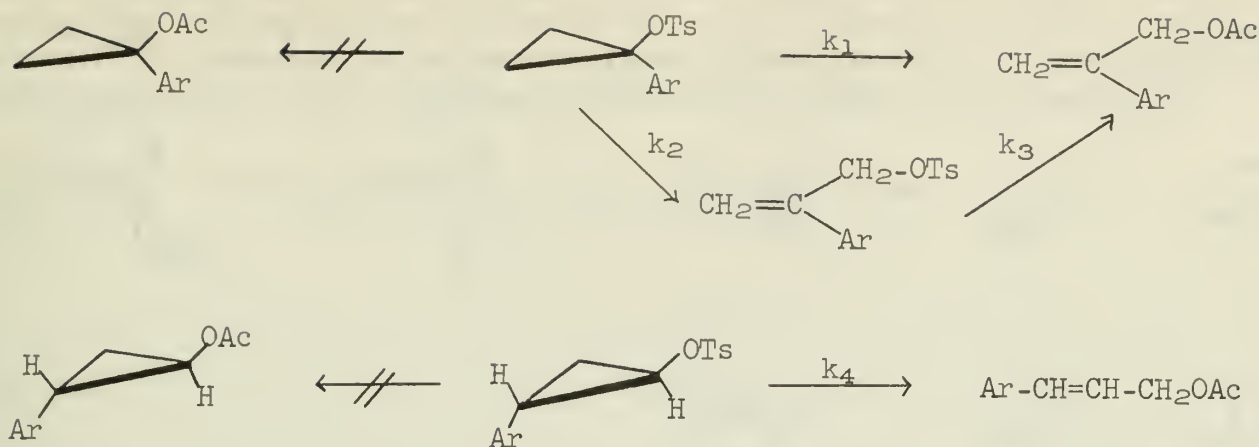
	70	4
	20	25
	300	25
	103	26
	1180	26
	379	26
	7340	26
	10 <sup>5</sup>	27

In the acetolysis of 1- and 2-phenylcyclopropyl tosylates<sup>25</sup> and chlorides<sup>28</sup> only the cinnamyl acetate was isolated although the corresponding cyclopropyl acetates were found to be stable to the reaction conditions. Acetolysis of 1-phenylcyclopropyl tosylate was complicated by internal return which indicated that ring-opening had occurred before the gegenion could diffuse away.<sup>25</sup> This solitary example of internal return in solvolyses of cyclopropyl derivatives suggests that this effect may be complicating other kinetic studies. Hammett  $\rho$ -values from correlations with  $\sigma^+$  were consistent with positive charge generation on C<sub>2</sub> of an ion intermediate between ions 1 and 2: -4.31 for  $k_1$ , -3.94 for  $k_2$ , and -1.75 for  $k_4$ .<sup>25</sup> From this study and related halonorcarane solvolyses, DePuy postulated concerted ionization and ring-opening with the groups trans to the leaving group moving outward. The interesting speculation was made that 3 gains stability owing to its resemblance to a cyclopropenyl cation without its C<sub>2</sub>-C<sub>3</sub>  $\sigma$ -bond, i.e. a cyclic system of two electrons in three  $\pi$ -orbitals.<sup>25</sup>

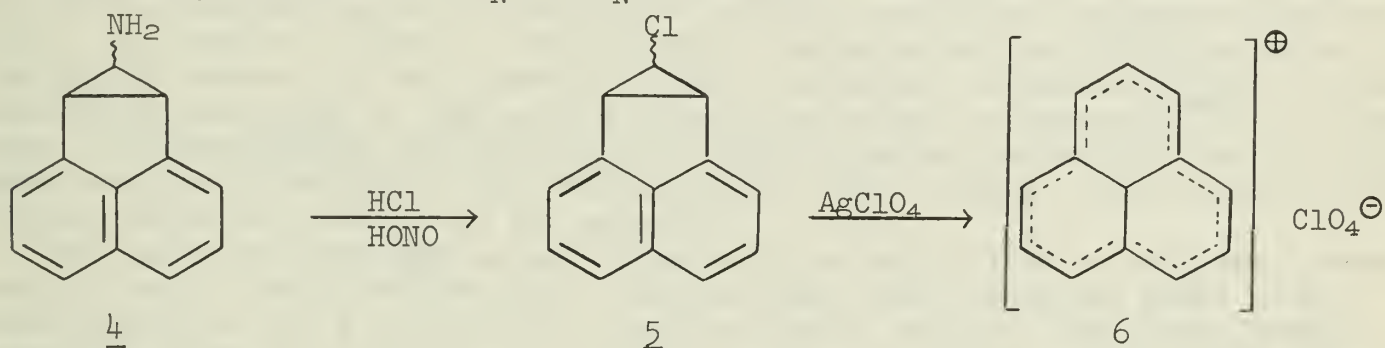
In addition to the numerous ring-opening solvolytic reactions of cyclopropyl derivatives, several anomalous examples from deamination studies have resulted in products retaining the cyclopropane ring. Deamination of apotricyclylamine<sup>29a</sup> and nortricyclylamine<sup>29b</sup> gave only the unrearranged alcohols, presumably because the bicycloheptyl system cannot accommodate a bridgehead double bond. No such restriction is operative in 3-amino-1,2-cyclopropanoacenaphthene (4) which gave only unrearranged





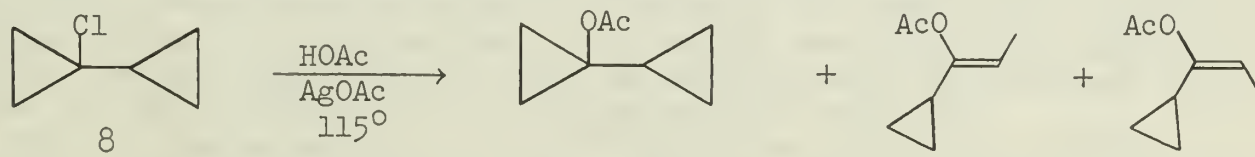


chloride (5) when deaminated in the presence of chloride ion.<sup>30a</sup> Ring-opening would have given the very stable perinaphthenyl cation (6), which was formed when 5 was treated with silver perchlorate. Pettit suggested an  $S_N1$ -type reaction of a diazonium chloride ion pair.<sup>30a</sup> It has been proposed that a free radical pathway is favorable for the decomposition of diazonium salts if the usual carbonium ion process is energetically costly;<sup>30b</sup> however, this interpretation has not received adequate experimental support. It has also been suggested that this reaction involves a cationic intermediate which is captured by a nucleophilic chloride ion prior to rearrangement, regardless of  $S_N1$  or  $S_N1$  mechanism.<sup>30c</sup>



Deamination of 7-aminonorcarane (7) was reported to yield only 7-hydroxynorcarane,<sup>31a</sup> but in a re-examination only cyclohepten-3-ol was isolated.<sup>31b</sup> At lower temperatures an unidentified alcohol, possibly a cyclopropanol, was obtained in very low yield.<sup>31b</sup> Scherer has reported that 4, 7, and trans-2-phenylcyclopropylamine each give the corresponding cyclopropyl chloride in very low yield upon treatment with nitrosyl chloride.<sup>31c</sup>

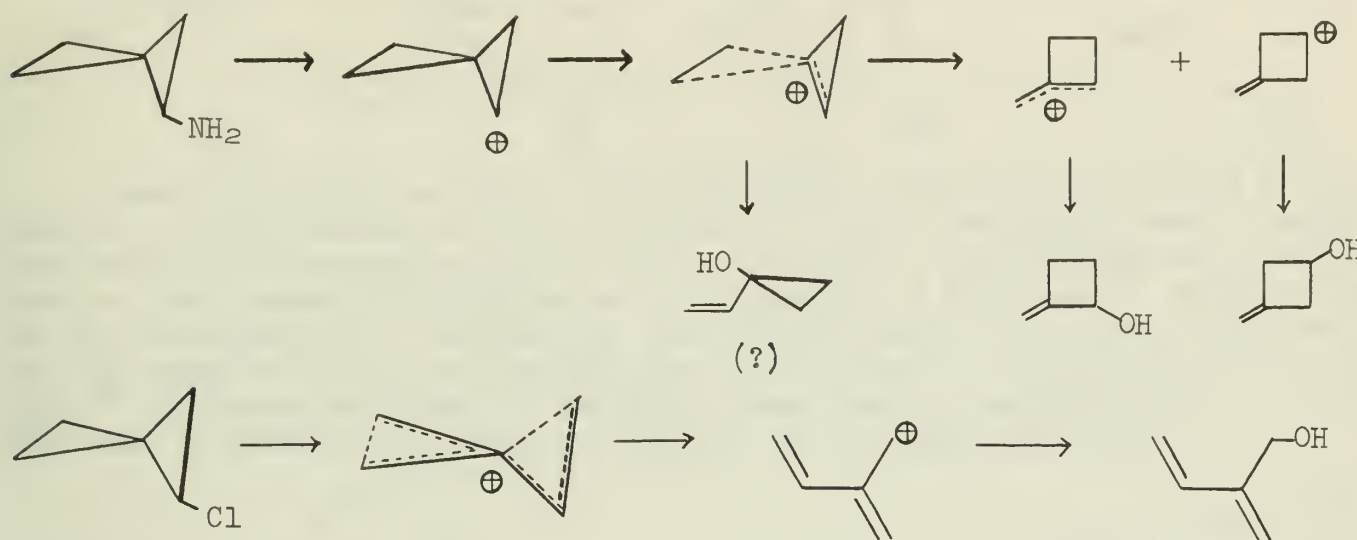
Kirmse has provided evidence for trapping of a cyclopropyl cation in very low yield from the decomposition of cyclopropyl diazonium ions.<sup>32</sup> Landgrebe and Becker isolated unrearranged acetate in 42.6% yield from the silver ion-assisted acetolysis of 1-chlorobicyclopentyl (8).<sup>33</sup> Owing to the intense conjugation of cyclopropane rings with carbonium ions<sup>1</sup> and the well-known behavior of the cyclopropylcarbinyl cationic system, the unique behavior of 8 was attributed to extensive charge delocalization in the initially-formed cation.



Corey has postulated that vibrationally excited ("hot") carbonium ions arise from deaminations by localization of recoil energy from loss of nitrogen.<sup>34</sup> Indeed, Applequist and coworkers have observed strikingly differing results in the deamination of spiropentyl amine<sup>35a</sup> and solvolysis of spiropentyl chloride.<sup>35b</sup> The former process was found to yield 2- and 3-methylenecyclobutanol while the latter gave exclusively 2-(hydroxymethyl)-1,3-butadiene. It was further determined that products from each reaction did not interconvert. These results suggested that deamination of spiropentyl



amine proceeded via a vibrationally excited, classical spiropentyl cation, while spiropentyl chloride solvolysis gave the normal "incipient allylic spiropentyl cation."<sup>35b</sup> Moreover, Konzelman confirmed these deamination products and also tentatively identified 1-vinylcyclopropanol as a reaction product.<sup>35c</sup>



#### STEREOCHEMISTRY OF THE ELECTROCYCLIC RING-OPENING

The elegant theory of Woodward and Hoffmann<sup>36a</sup> and state correlation diagrams<sup>36b</sup> predict the thermal, concerted ionization and ring-opening of cyclopropyl derivatives to be a disrotatory process. Extended Hückel molecular orbital (EHMO) calculations distinguish between the two symmetry-allowed disrotatory processes in that the one where the groups trans to the leaving group move outward is favored.<sup>36a,37</sup> In this manner the developing 2p-orbitals on the terminal carbons can provide overlap with the developing 2p-orbital on the central carbon, thus forming a three-center bonding interaction on the backside of the molecule.

The more elaborate EHMO calculations by Kutzelnigg<sup>37</sup> were in complete agreement with Hoffmann's results<sup>36a</sup> and also indicated that ion 1 could not exist since rearrangement to ion 2 would require zero activation energy. The lowest energy transition state was calculated to involve turning of CH<sub>2</sub> groups 45°, rather than 0° or 90°, to the C<sub>1</sub>-C<sub>2</sub>-C<sub>3</sub> plane in the preferred disrotatory direction.<sup>37</sup>

The most extensive kinetic investigations of the above predictions were performed by Schleyer, Schöllkopf, and coworkers.<sup>23,38</sup> Results of EHMO calculations<sup>36,37</sup> and DePuy's postulate<sup>25</sup> both predict trans,trans-2,3-dimethylcyclopropyl tosylate (9) to give rise to the trans,trans-dimethylallyl cation and cis,cis-2,3-dimethylcyclopropyl tosylate (10) to give the more strained cis,cis-cation. In support of this Schleyer and Schöllkopf found that at 150° 9 undergoes acetolysis 4500 times faster than 10.<sup>23</sup> In all monocyclic cases studied the above prediction held: the isomer with bulky alkyl groups trans to the leaving group reacted faster. In fact Schleyer obtained reasonable agreement with observed rate constants by means of calculations based on empirical steric and electronic factors.<sup>4,23</sup>

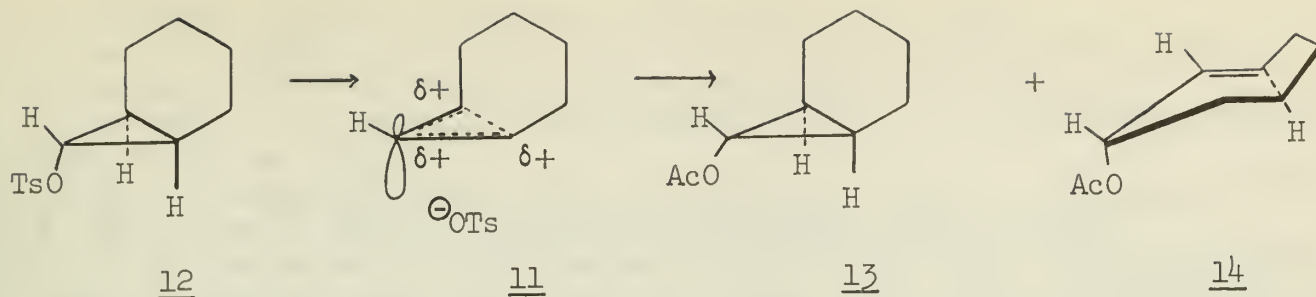
In the bicyclic cyclopropyl tosylate series, the above reactivity is reversed since it is energetically more costly to rotate carbon-carbon bonds outward than it is to rotate carbon-hydrogen bonds.<sup>38</sup> This trend is dramatically demonstrated by an endo/exo rate ratio of greater than 2.5 x 10<sup>6</sup> for acetolysis of bicyclo[3.1.0]hexyl tosylate. In the endo bicyclic series the rate increases as the fused ring becomes smaller and the converse holds in the exo bicyclic series.<sup>38</sup>

When the leaving group is situated exo to the fused ring, complete ring-opening to a flat allyl cationic intermediate is unlikely on steric grounds. Schleyer and Schöllkopf propose a special "half-opened" intermediate (11) with the vacant orbital on the exo side only.<sup>37,38</sup> Since the pyramidal configuration at C<sub>2</sub> is retained, the nucleophile approaches from the same side where the leaving group departed. This intermediate has received both theoretical<sup>37</sup> and experimental support,<sup>38,39</sup> and it possibly explains some previously anomalous deamination results.<sup>29-31</sup> Thus acetolysis of 12 gave 13 and the 1,3-diacetate from reaction of acetic acid with 14.

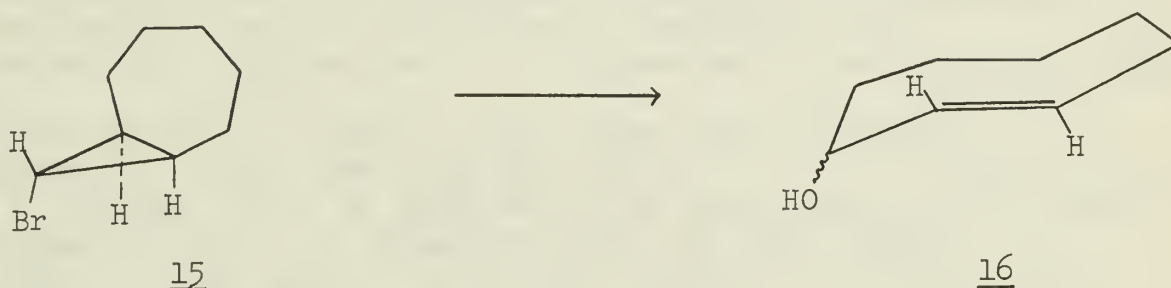




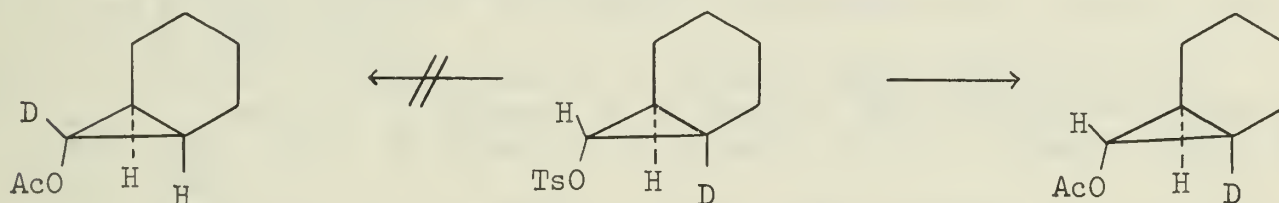




Kutzelnigg points out that this "half-opened" cation (11) is fixed in the geometry of the transition state by steric constraint and should have a certain life-time since it is energetically near the allyl cation. EHMO calculations further predict equal charge distribution at C<sub>1</sub>, C<sub>2</sub> and C<sub>3</sub> of this ion.<sup>37</sup> Further support for this intermediate is provided by the fact that silver ion-assisted solvolysis of exo-8-bromobicyclo[5.1.0]octane (15) leads exclusively to trans-cycloocten-3-ol (16).<sup>39</sup> Although solvolysis of the endo isomer has not been reported, it would be predicted to undergo more facile solvolysis to the cis-cyclooctenol.



Schleyer and Schöllkopf have ruled out neighboring group participation by the C<sub>1</sub>-C<sub>2</sub> or C<sub>5</sub>-C<sub>6</sub> σ-bond in the exo-norcaryl series:<sup>4,38</sup>



The above selection rules are rigorously obeyed in all reported cases of thermal ring-openings of cyclopropyl tosylates,<sup>3</sup> cyclopropyl halides,<sup>7,40-43</sup> and gem-dihalocyclopropanes.<sup>44-55</sup>

The one reported example<sup>56</sup> of a violation of the selection rules was re-examined<sup>57,58</sup> and found to have erroneous stereochemical assignments.

## CONCLUSION

Despite the apparent inertness of cyclopropyl derivatives toward solvolysis, significant anchimeric assistance appears to be present. Extensive solvolysis studies and theoretical predictions make it highly unlikely that the transition state looks like 1, except possibly in "hot" carbonium ion reactions such as deaminations. Kinetic data supported by theoretical calculations suggest concerted ionization and ring-opening with the groups trans to the leaving group moving outward and proceeding through a transition state intermediate between ions 1 and 2. In spite of the numerous kinetic investigations supporting the above theoretical predictions, there has not appeared an unambiguous stereochemical proof for one disrotatory mode operating in preference to the other, or even in preference to conrotatory ring opening.

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THE MEASUREMENT AND INTERPRETATION OF  
THE RATES OF INVERSION ABOUT NITROGEN

Reported by Clayton T. Mabuni

March 25, 1968

The rates of inversion about nitrogen have been obtained from various physical methods and interpreted in qualitative terms of the collision and harmonic oscillator models for several nitrogen compounds. The inversion of nitrogen is a unique process in that, at one extreme, it is a molecular vibration and, at the other extreme, when it is sufficiently slow, it can be interpreted as an isomerization reaction. Factors affecting the vibrational ground state energies and the energies of activation of the inversion process are of great interest since they determine the stereochemistry about nitrogen.

METHODS

A. Nmr spectroscopy. The temperature-dependent nmr spectra of benzylmethylamine 7 (see Table I) and of all the aziridines and some of the imines covered in this seminar have been studied.

The divergence of the methylene group of the benzylmethylamine 7 from a singlet to an AB system was explained as being due to the slowing down of the inversion rate making the  $\text{CH}_2\text{N}(\text{CH}_3)\text{OCH}_3$  group a  $\text{CH}_2\text{NABC}$  system<sup>1</sup>.

The aziridine inversions (Tables II and III) were observed by watching the coalescence of the ring methylenes or gem-dimethyl groups or both. The spectra of aziridines without substituents on C2 or C3 were observed to give  $A_2B_2$  or  $AA'BB'$  spectra. When gem-dimethyl groups were observed, the single methyl signal was resolved into two signals below the coalescence temperature. For the fluoro-substituted aziridines similar observations were reported using  $^{19}\text{F}$  nmr studies.

Temperature-dependent nmr spectra of the imines showed a singlet being resolved to a doublet for the p,p'-dimethoxybenzophenone imines 37<sup>2</sup> (see Table IV). The same phenomenon occurred for the N-methyl group in the imines 30.<sup>3</sup>

Calculations<sup>4</sup> of  $k$ , the rate of inversion at the coalescence temperature  $T$ , were generally made by using the equation

$$k = \pi \nu_{AB} / \sqrt{2},$$

where  $\nu_{AB}$  is the difference in chemical shifts of protons A and B. Calculations employing the line-width methods required use of the following equation<sup>5</sup>

$$k = \pi ( \nu_{AB}^4 + 2 \nu_{AB}^2 \Delta \nu^2 - \Delta \nu^4 )^{1/2} / 2 \Delta \nu$$

in order to obtain the rate of inversion above the coalescence temperature. Here  $\Delta \nu$  is the full line width in cycles per second at half height.

The data secured through temperature-dependent nmr studies were coalescence temperatures, rates and free energies of activation at the coalescence temperature, and, less frequently, energies of activation and the Arrhenius constant. (The energy of activation  $E_a$  and the Arrhenius constant  $A$  are defined by the rate equation  $k = A \exp -E_a/RT$ , where  $k$  is the rate constant and  $T$  is the temperature.) Although the values of the Arrhenius constant reported were not in the normal range, i.e., greater than  $10^{11.5} \text{ sec}^{-1}$  but less than  $10^{14.5} \text{ sec}^{-1}$ ,<sup>6</sup> it was assumed that the errors were systematic<sup>7</sup> as indicated by carefully conducted studies on hindered rotation in the amides<sup>8</sup>. Thus, the reaction is assumed to have a nearly constant and small entropy of activation and that the rate observed is the inversion rate about nitrogen.

Comparisons have been made of the temperature at which several compounds have the same inversion rate.

B. Flash photolysis-ultraviolet studies. Using a high intensity light source for short periods of time, Wettermark and Dogliotti<sup>9</sup> excited imines 35 and 36, then





observed changes in the ultraviolet absorption spectrum indicative of the disappearance of photolytically generated species as a function of time. The dark-reaction decay of one of the new absorptions was observed to follow first-order reaction kinetics and was found to be insensitive to acid catalysis and nearly so to base catalysis. (The phenolic group in the imines 36 could be ionized and different rates could be assigned to the cis-trans isomerization of the acid and its conjugate base). The ultraviolet absorption spectra indicated that quinoid forms did not intervene in the reaction, since they could be observed by following the change in another ultraviolet absorption band produced by photolysis whose decay was subject to acid and base catalysis and was of a different kinetic order. The observed reaction, postulated to be the thermal isomerization of the photolytically generated cis-form to the trans-form, gave Arrhenius parameters of the barrier from the energy well of the cis-form, and established a lower limit on the energy of activation for nitrogen inversion in these imines.

C. Ultraviolet studies.<sup>2,3</sup> In the cases where the imines could be shown by other physical methods to exist as a single imine isomer in the solid form, the change in ultraviolet absorption occurring for the isomerization in solution was followed. Equilibrium studies were conducted by nmr.

D. Infrared studies<sup>2,3</sup>. Studies to set lower limits on the energy of activation of the imine 39 were conducted by observing the appearance and disappearance of the infrared bands attributable to the trans or the cis isomers in potassium bromide pellets. Thermal isomerizations were conducted by heating the pulverized pellet and observing the infrared spectrum for changes. These infrared studies were conducted together with nmr and ultraviolet studies which supported the identification of the phenomenon being observed as cis-trans isomerization of the imines.

## RESULTS

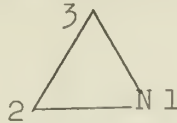
Table I. Nitrogen Inversion in the Amines.

Compound	Structure	Ea,			Ref
		kcal mole <sup>-1</sup>	Method <sup>a</sup>		
<u>1</u>	NH <sub>3</sub>	5.81	Microwave		b
<u>2</u>	N(CH <sub>3</sub> ) <sub>3</sub>	7.46	Calc		c
<u>3</u>	C <sub>6</sub> H <sub>5</sub> NH <sub>2</sub>	< 0.3	Microwave		d
<u>4</u>	$\overline{\text{C}_4\text{H}_4\text{NH}}$	0 (planar)	Microwave		e
<u>5</u>	HCONH <sub>2</sub>	1.1	Microwave		f
<u>6</u>	H <sub>2</sub> NCONH <sub>2</sub>	0 (planar)	X-ray		g
<u>7</u>	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> N(CH <sub>3</sub> )OCH <sub>3</sub>	12.9 ± 0.3 <sup>k,1</sup>	A		h
<u>8</u>	C <sub>6</sub> H <sub>5</sub> NHSi(CH <sub>3</sub> ) <sub>3</sub>	> 0 (pyramidal)	A		i
<u>9</u>	(CH <sub>3</sub> ) <sub>2</sub> NSO <sub>2</sub> N(CH <sub>3</sub> ) <sub>2</sub>	> 0 (pyramidal)	X-ray		j

<sup>a</sup>See Methods. <sup>b</sup>See ref 14. <sup>c</sup>See ref 12. <sup>d</sup>See ref 24. <sup>e</sup>See ref 27. <sup>f</sup>See ref 28. <sup>g</sup>See ref 29. <sup>h</sup>See ref 1. <sup>i</sup>See ref 34, 35. <sup>j</sup>See ref 37. <sup>k</sup>Determined in 20% (w/v) hexane solutions. The common logarithm of the Arrhenius constant was 12.8 ± 0.3 sec<sup>-1</sup>.



Table II. The Relative Rates of Inversion in the NC Bonded Aziridines.<sup>a,b</sup>

Compound	Substituent (s) on aziridine	 Temp, °C at which $k \approx 60 \text{ sec}^{-1}$	Ea, kcal mole <sup>-1</sup>	A <sub>2,1</sub> sec <sup>-1</sup>	Ref
<u>10</u>	1-CH <sub>3</sub>	150	19 ± 3	10 <sup>11</sup>	c
<u>11</u>	1-C <sub>2</sub> H <sub>5</sub>	108			d
<u>12</u>	1-C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub>	105			d
<u>13</u>	1-C <sub>6</sub> H <sub>5</sub> (CH <sub>2</sub> ) <sub>2</sub>	96			d
<u>14</u>	1-cyclo-C <sub>6</sub> H <sub>11</sub>	95			d
<u>15</u>	1- <sup>1</sup> H		11.0 <sup>1</sup>		e
<u>16</u>	1- <sup>2</sup> H		14.3 <sup>1</sup>		e
<u>17</u>	1-t-C <sub>4</sub> H <sub>9</sub>	> rm temp			f
<u>18</u>	1,2,2-(CH <sub>3</sub> ) <sub>3</sub>	97	10.0	10 <sup>7</sup>	g
<u>19</u>	trans-1-C <sub>2</sub> H <sub>5</sub> -2,3- (CH <sub>3</sub> ) <sub>2</sub>	90			d
<u>20</u>	1-C <sub>2</sub> H <sub>5</sub> -2-CH <sub>2</sub>	-65			d
<u>21</u>	1-CH <sub>3</sub> -2-CH <sub>2</sub>	-103	6.4	10 <sup>9</sup>	g
<u>22</u>	1-C <sub>6</sub> H <sub>5</sub>	-60 <sup>j</sup>			d
<u>23</u>	1-(CH <sub>3</sub> ) <sub>2</sub> NCO	-40 <sup>k,m</sup>			h
<u>24</u>	1-CF <sub>3</sub> -2,2-F <sub>2</sub>		5.5 ± 0.5	10 <sup>8</sup>	i

a

Table after that in ref 19. <sup>b</sup>Data from nmr of pure liquid unless otherwise noted.  
<sup>c</sup>See ref 15. <sup>d</sup>See ref 16. <sup>e</sup>See ref 38. <sup>f</sup>See ref 18. <sup>g</sup>See ref 20. <sup>h</sup>See ref 7.  
<sup>i</sup>See ref 30. <sup>j</sup>Rate of inversion was 42 sec<sup>-1</sup>. <sup>k</sup>Rate of inversion was ca. 10 sec<sup>-1</sup>.  
<sup>l</sup>Data from nmr of 25% carbon tetrachloride solutions. <sup>m</sup>Data from nmr of vinyl chloride solution.

Table III. Nitrogen Inversion in the N-Heteroatom Bound Aziridines.

Compound	Substituent on Aziridine	Coalescence T, °C	Ref
<u>25</u>	1-Cl	180 <sup>d</sup>	a
<u>26</u>	1-Br	140 <sup>d</sup>	a
<u>27</u>	1-Cl-2,2-(CH <sub>3</sub> ) <sub>2</sub>	120 <sup>e</sup>	b
<u>28</u>	1-Cl-2-(CH <sub>3</sub> )	isolated isomers	c
<u>29</u>	1-Cl-2,3-(CH <sub>2</sub> ) <sub>4</sub>	isolated isomers	a

<sup>a</sup>See ref 39. <sup>b</sup>See ref 40. <sup>c</sup>See ref 41. <sup>d</sup>Solvents, if any, were not indicated.  
<sup>e</sup>Data from nmr in 25% (w/v) carbon tetrachloride solution.





Table IV. Data on the Unimolecular Cis-trans Isomerization of Imines<sup>a</sup>.

$\begin{array}{c} \text{A} \\ \diagup \\ \text{B} \end{array} \text{C} = \text{NX}$				Sol-vent	k, sec <sup>-1</sup>	Ea, kcal mole <sup>-1</sup>	Method <sup>b</sup>	Ref
30	p-XC <sub>6</sub> H <sub>4</sub>	p-XC <sub>6</sub> H <sub>4</sub>	CH <sub>3</sub>	l	10 <sup>-4</sup>	25-27	A	c
31	CH <sub>3</sub>	CH <sub>3</sub>	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub>	m	-	> 23	A	d
32	o-RNHAr	C <sub>6</sub> H <sub>5</sub>	R <sub>2</sub> N(CH <sub>2</sub> ) <sub>2</sub>	-	<< 10 <sup>-4</sup>	-	isolated	e
33	o-CH <sub>3</sub> NHAr	C <sub>6</sub> H <sub>5</sub>	CH <sub>3</sub>	-	-	-	isolated	f
34	CF <sub>3</sub>	CF <sub>3</sub>	(CF <sub>3</sub> ) <sub>2</sub> CF	n	10 <sup>3</sup>	13	A	g
35	C <sub>6</sub> H <sub>5</sub>	H	C <sub>6</sub> H <sub>5</sub>	o	-	16-17	B	h
				p	20	16.5	B	i
36	o-HOC <sub>6</sub> H <sub>4</sub>	H	C <sub>6</sub> H <sub>5</sub>	p	10	14.2	B	i
37	p-X'C <sub>6</sub> H <sub>5</sub>	p-XC <sub>6</sub> H <sub>4</sub>	p-YC <sub>6</sub> H <sub>4</sub>	l, q	10	17-20	B	j
38	CH <sub>3</sub>	CH <sub>3</sub>	C <sub>6</sub> H <sub>5</sub>	m	10 <sup>-1</sup>	21	A	k
39	p-ClC <sub>6</sub> H <sub>4</sub>	C <sub>6</sub> H <sub>5</sub>	Br	l	< 10 <sup>-6</sup>	-	C, D	j
40	p-ClC <sub>6</sub> H <sub>4</sub>	C <sub>6</sub> H <sub>5</sub>	Cl	l	< 10 <sup>-8</sup>	-	C	j
41	p-ClC <sub>6</sub> H <sub>4</sub>	C <sub>6</sub> H <sub>5</sub>	CH <sub>3</sub> O	r	< 10 <sup>-13</sup>	-	C	j

<sup>a</sup>Table after that in ref 2. <sup>b</sup>See Methods. <sup>c</sup>See ref 3. <sup>d</sup>See ref 21. <sup>e</sup>See ref 22. <sup>f</sup>See ref 23. <sup>g</sup>See ref 33. <sup>h</sup>See ref 31. <sup>i</sup>See ref 9, 32. <sup>j</sup>See ref 2. <sup>k</sup>See ref 32. <sup>l</sup>Cyclohexane. <sup>m</sup>Quinoline. <sup>n</sup>Neat. <sup>o</sup>Methylcyclohexane. <sup>p</sup>Ethanol. <sup>q</sup>Carbon tetrachloride. <sup>r</sup>Decane.

Some results from studies on amines are compiled in Table I; those for the aziridines are summarized in Tables II and III and those of the imines in Table IV.

The compounds studied have had such different structural features that they did not show an obvious pattern; however, the greater control of variables in the aziridines has allowed more detailed conclusions. In Table II the compounds can be naturally subdivided into two groups according to their coalescence temperatures and their structure---(a), which is designated normal and (b), in which lone pair  $\pi$ -bonding is possible with adjacent carbon  $\pi$ -M.O.'s. The separation of the aziridines in Table III is made since the change in the bond force constants of the NC versus the N-heteroatom bonds may be significant.

If the organization of the aziridines into normal and possible  $\pi$ -bonded and heteroatom-bonded systems is applied to the data on imines in Table IV, similarities of the behavior of an imine with the corresponding aziridines become apparent. The most obvious comparison involves the N-halogen bound compounds, which in both series are configurationally stable. A second glance at the N-aryl compounds in both cases suggests a lower barrier to inversion relative to the respective normal compounds. If the imines and aziridines appear to be so related, the patterns may be apparent in the amines, too. The fact that very few dynamic studies have been undertaken for the amines forces us to look to static studies for data. Barriers are present in the normal amines, but not in all of the cases where the lone pair of electrons can bond with  $\pi$ -orbitals on N-bonded carbons. The observance of a high barrier for 7 by nmr is as striking as the stability of the haloaziridines and the haloimines.

Three major divisions of the subject matter are thus appropriate: (a) cases with nitrogen bonded to simple n-alkyl groups, (b) cases where the lone pair electrons on nitrogen may interact with partially filled M.O.'s on the nitrogen-bound carbon atoms and (c) cases where nitrogen is bound to a heteroatom.

## DISCUSSION

In the inversion process in the amines and aziridines, nitrogen vibrates back and forth through the plane described by the bonded atoms. In the imines the same process consists of the "wagging" of the N-substituent in the plane of the imino





function, the plane described by ABCN in ABC=NX.

The inversion energy barriers for simple symmetrical molecules of the type  $AX_3$ , e.g., ammonia, may be calculated in terms of a point-mass, nonrotating harmonic oscillator model.<sup>10</sup> The potential energy of the system  $V$  is then a function of the reduced mass of the system  $\mu$  and the frequency leading to inversion about nitrogen  $\nu$ , included in the force constant  $k$ , and the square of  $x$ , the difference of the absolute value of the average displacement from the absolute value of the displacement of nitrogen from the plane of its substituents ( $V = 2^{-1} kx^2$ ). Kincaid and Henriques<sup>10</sup> applied the function to the aziridines, and asserted that although the magnitudes of the energy barriers calculated for ammonia (11 kcal/mole), trimethylamine (15 kcal/mole) and 1-methyl-aziridine (1-methyl-Az, 38 kcal/mole) were off, the relative values should be reasonable. Refinement<sup>11</sup> of the simple model has been made by the addition of a harmonic oscillator term for the angular displacement and reasonable values have been obtained<sup>11</sup> for the molecules ammonia, arsine and phosphine, although attempts<sup>12</sup> to apply it to the aziridines and imines are as qualitative as in the calculations employing the simpler function.

Since the inversion frequencies of the aziridines and imines are decreased considerably compared to the amines, the Arrhenius equation may be applied to the study of the inversion processes in the more complex aziridine and imine systems.

In contrast to the harmonic oscillator model in which electromagnetic excitation of the molecule occurs, the collision model employs bimolecular collisions to supply the molecule that is to invert with the energy of activation required to cross the barrier to inversion<sup>13</sup>.

Since the inversion is a vibrational motion, it is assumed that the energy of activation is a complex function of the force constants of the nitrogen-substituent atom bonds and bond angles.

Thus, the conformational stability of the lone pair is determined primarily by the force constants <sup>and displacements of the atoms</sup> of the inverting system. Comparisons of energies of activation for inversion in different compounds with similar force constants <sup>and displacements of the atoms</sup> may then be rationalized relative to a standard in terms of factors lowering or raising the energy of activation for inversion.

The factors affecting the energy of activation for inversion of nitrogen were summarized<sup>7</sup> as being (a) steric effects, including nonbonded repulsive interactions, (b) inductive effects which by more electronegative substituents causes the other orbitals including that of the lone pair to acquire greater s character, (c) conjugative effects and (d) electrostatic effects in which lone pair electrons repulse lone pairs on substituent atoms.

#### NORMAL AMINES, AZIRIDINES AND IMINES

Normal energies of activation are assigned to the simple amines, aziridines and imines. Using the equation of Costain and Sutherland<sup>11</sup>, Koeppl, et.al.<sup>12</sup> calculated inversion barriers of 5.58 kcal/mole for ammonia and 7.46 kcal/mole for trimethylamine. Experimentally a barrier of 5.81 kcal/mole<sup>14</sup> has been found for ammonia.

The energies of activation for the 1-alkyl-Az were greater than those in the alkylamines. Aziridine 10 was found to have a barrier of 19.3 kcal/mole<sup>15</sup>. The temperatures<sup>16</sup> for inversion rates of ca. 60 sec<sup>-1</sup> for aziridines 11, 12, 13 and 14 were 108° 105°, 96° and 95°.

Steric effects, if any, might be detected in the aziridine 17. The first studies reported no coalescence at temperatures down to -77°<sup>16,17</sup>; however, in recent studies<sup>18</sup>, the methylene protons of 17 were found to coalesce at room temperature.

Anet and Osyany<sup>19</sup> suggested that the steric factor might be approximated by appropriate alkyl substituents at positions two and three on the 1-alkyl-Az. Aziridine 18<sup>20</sup> was reported to have an energy of activation of 10 kcal/mole. Aziridine 19 had an inversion rate of ca. 60 sec<sup>-1</sup> at 90°<sup>20</sup>.

If the steric approximation holds, it might appear that the barriers to inversion are about normal. It is suggested, however, that since in the case of a steric effect the energy of the ground state is raised, the change observed is a decrease in the magnitude of the energy of activation. The energy barrier relative to the ground state of the corresponding aziridine in which steric effects are not as great should





be about the same. The effects might therefore be observed in the difference in magnitudes of the energies of activation of 1-butyl-Az and aziridine 17 rather than in a comparison of the temperatures at which the rates are equal.

The energy of activation for imine 30 was found to be greater than 23 kcal/mole<sup>21</sup> for 31 it was 25-27 kcal/mole and for 32 and 33 it was large enough so that they could be isolated<sup>22,23</sup>. Curtin and Hauser<sup>3</sup> found by using Hammett relationships that rates of 30 were little affected by substituents on the aryl group attached at the carbon atom of the imine so that conjugation with the aryl groups appears negligible.

#### LONE PAIR ELECTRON INTERACTIONS WITH N-BOUND CARBON $\pi$ -MO'S

Inversion in the amines, aziridines and imines in which the lone pair electrons can be delocalized over neighboring  $\pi$ -systems might be expected to lower or eliminate the inversion barrier. Four examples of amines may be considered: aniline, pyrrole, formamide and urea. Microwave spectroscopic<sup>24</sup>, dipole moment data<sup>25</sup>, and other results<sup>26</sup> indicate that the configuration about nitrogen in aniline is pyramidal. The barrier to inversion appears to be less than 0.3 kcal/mole indicating substantial resonance stabilization of the planar transition state.

In pyrrole the delocalization energy of the lone pair electrons to produce an aromatic system is enough to offset the repulsive energies of delocalizing the lone pair on nitrogen so that the molecule was found to be planar<sup>27</sup>.

Formamide was found to be nearly planar with an inversion barrier of 1.1 kcal/mole<sup>28</sup>. Urea appeared to be planar by X-ray crystallography<sup>29</sup>. The low inversion barriers suggested by the nearly planar structures of these molecules indicated a fine balance between bonding forces and repulsions in the planar configuration.

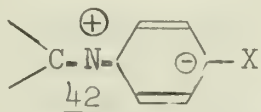
Studies conducted on aziridines in which the lone pair electrons could overlap with olefinic, aryl and carbonyl groups indicate a lowered barrier to inversion. Aziridine 20<sup>16</sup> was observed to have a rate of inversion of ca. 60 sec<sup>-1</sup> at -65°. Aziridine 21<sup>20</sup> was observed to have an energy of activation of 6.4 kcal/mole. Aziridine 22<sup>16</sup> gave a coalescence temperature of -65° for an inversion rate of ca. 60 sec<sup>-1</sup>.

Investigation of aziridine 23 was complicated by the possibilities of hindered rotation and nitrogen inversion<sup>7</sup>. Moment analysis of the ring methylene AA'BB' system indicated that the splitting of the protons from -40° and below was due to slow inversion of nitrogen.

Aziridine 24<sup>30</sup> is included in this section because of its low energy of activation, and because hyperconjugation in which fluorine carries a negative charge might be important. If hyperconjugation is the reason for lowering the energy barrier, the planar molecule must be able to more effectively interact with fluorine.

The N-arylimines are reported to have lower inversion barriers than the N-alkylimines. Imines 35, 36, 37 and 38 have energies of activation of 14-21 kcal/mole<sup>21,31,32</sup>. Hammett parameters for para substituents on the aryl groups in 37<sup>2</sup> indicate that conjugation of the form 42 is important, implying enough delocalization in a planar configuration to lower the energy of the transition state species.

Like 24 the perfluoroimine 34<sup>33</sup> has a lower barrier to inversion than the corresponding alkylimines. The factors responsible for the lowering of the energy barriers in the fluoroaziridine appear to be operating in this perfluoroimine, too.



#### LONE PAIR ELECTRON INTERACTION WITH N-BOUND HETEROATOMS

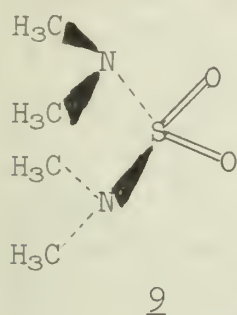
The systems in which nitrogen is bound to heteroatoms are somewhat more complex; the variables are not understood as well as in the previous systems. Benzylmethylamine 7 showed a barrier to inversion of 12.9 ± 0.3 kcal/mole in *n*-hexane solution<sup>1</sup>. The large energy of activation appears to be reasonably rationalized by considering the electrostatic repulsions of the lone pair electrons and inductive effects.

In amines bonded to the second-row elements silicon, sulfur, and chlorine possible (p→d) $\pi$ -bonding interaction depends on the energies of the low-lying d-orbitals, their distance from the lone pair electrons on nitrogen and other factors. N-(Trimethylsilyl)-aniline (8) has been found to be hybridized as in aniline according to the <sup>15</sup>NH coupling constant relationship for hybridization at nitrogen<sup>34</sup> and according to the





ortho-para fluorine coupling constant relationship with the chemical shift of the para fluorine in pentafluorophenylamine and N-(trimethylsilyl)-pentafluorophenylamine<sup>35</sup>. That significant overlap of the d-orbitals can occur with the  $sp^3$  hybridized lone pair electron orbitals was shown in a calculation<sup>36</sup>. The fact that greater bonding is expected by ( $p \rightarrow d$ )  $\pi$ -bonding suggests that other factors are also important.



Sulfonamide 9<sup>37</sup> has an  $\angle CNC = 112.9^\circ$  and an  $\angle SNC = 119^\circ$ . The separation of the nitrogen from the plane of the SCC atoms bound to it was 0.27 Å, compared to 0.51 Å calculated for a pyramidal geometry, indicating ( $p \rightarrow d$ )  $\pi$ -bonding. Since the nitrogen is nearer to the plane of the SCC atoms bound to it, the energy of the transition state for inversion would be lower than in the non- ( $p \rightarrow d$ )  $\pi$ -bonding state in which nitrogen would be pyramidal.

Investigations of aziridines in which heteroatoms are bonded to nitrogen have been carried out with the isotopically substituted-aziridines 15 and 16 and the halogen-substituted compounds.

The change from a proton to a deuteron is primarily one of mass. The energies of activation<sup>38</sup> were 11.0 kcal/mole for 15 and 14.3 kcal/mole for 16; the difference should approximate the difference in ground state vibrational energies for nitrogen inversion.

Aziridines 25 and 26 and their ring alkylated derivatives have been found to have high barriers to inversion, although an earlier report had indicated low barriers.<sup>17</sup> Coalescence of the ring methylene proton absorptions occurred above room temperature for 25<sup>38</sup> and for 1-chloro-2,2,3,3-tetramethyl-Az.<sup>40</sup> The coalescence temperature of aziridine 27<sup>39</sup> was reported to be greater than 180°. Additional support for the configurational stability of the halo-aziridines comes from the reports of isolation of nitrogen stereoisomers of aziridines 28<sup>41</sup> and 29<sup>39</sup>.

Curtin and his coworkers<sup>2</sup> were the first to investigate the rates of isomerization of N-methoxy and N-haloimines. Both N-heteroimines could be heated for prolonged periods with no indication of isomerization.

The fact that no energies of activation for the aziridine and imine N-heteroatom bonded compounds have been reported does not permit comparison with the normal compounds. The apparently high energy barriers could be due to unusually low ground state energies rather than to unusual destabilization of the transition state.

## CONCLUSION

Many assumptions were made since the data presented were generally not obtained primarily for the purposes used in this seminar. The interpretation of the evidence for the carbon-bonded nitrogen compounds appears to be satisfactory in terms of resonance and steric effects. For the heteroatom-bound nitrogen compound that permitted comparison, inductive and electrostatic effects appeared suitable for rationalizing an unusual energy of activation.

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## ACID-CATALYZED KETONE ISOMERIZATIONS

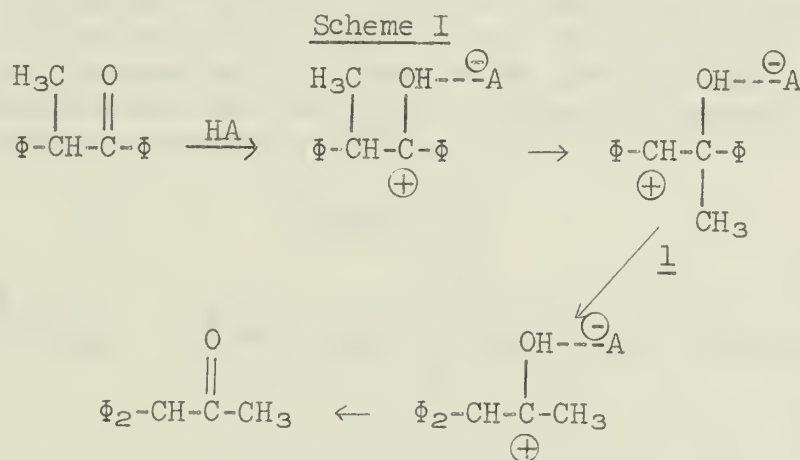
Reported by Richard E. Peavy

March 28, 1968

The acid-catalyzed isomerization of ketones and the pinacol rearrangement<sup>1</sup> are examples of carbonium ion rearrangements involving 1,2-shifts. Until recently, little quantitative study has been devoted to ketone isomerizations and early investigators relied heavily on product studies to determine the course of a reaction. More recent labeling experiments have revealed that several mechanisms are operative in the isomerizations, depending upon the structure of the ketone being studied and the reaction conditions employed. The purpose of this seminar will be to examine the various mechanistic proposals that have been suggested for ketone isomerizations and evaluate their significance on the basis of recent labeling and nmr studies. The seminar will also relate the importance of structure and reaction conditions in the interpretation of isomerization mechanisms and discuss the concept of isomerization via the most stable carbonium ion.

## AROMATIC AND BRANCHED-CHAIN ALIPHATIC KETONES

The first ketone isomerization was reported by Favorskii in 1926 when he found that isobutyrophenone on heating with zinc chloride produced 3-phenyl-2-butanone.<sup>2</sup> The same transformation was observed with pivalophenone and *t*-amylphenone to give 3-methyl-3-phenyl-2-butanone and 3-methyl-3-phenyl-2-pentanone respectively.<sup>3</sup> In a similar study Zalesskaya found that treatment of  $\alpha$ -phenylpropiophenone and of  $\alpha$ -methylbutyrophenone with zinc chloride at elevated temperatures resulted in the formation of 1,1-diphenylpropanone and 3-phenyl-2-pentanone respectively.<sup>4,5</sup> No other isomers were isolated. Zalesskaya proposed that the isomerization proceeded with initial protonation of the carbonyl oxygen to give a complex of the conjugate



acid of the ketone. This was followed by methyl and phenyl migrations to give the observed product (Scheme I).<sup>4</sup>

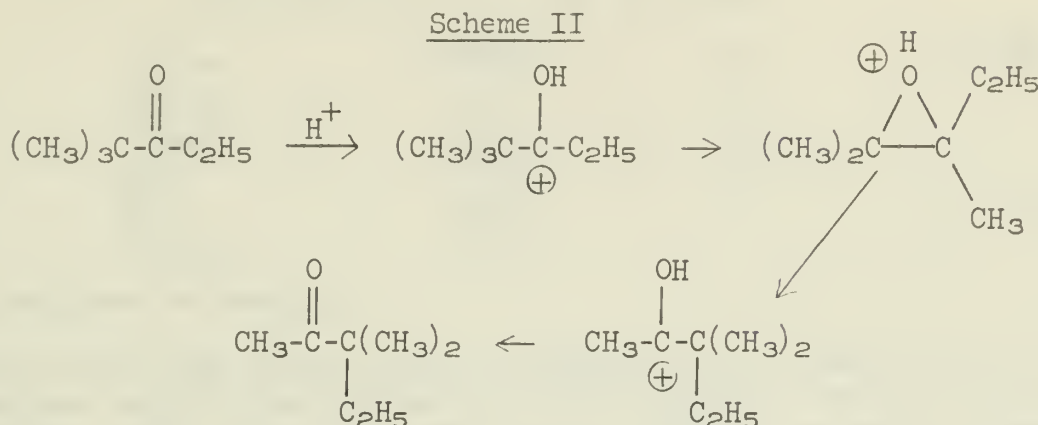
A more detailed study of the zinc chloride isomerization of  $\alpha$ -methyl- $\alpha$ -ethylbutyrophenone revealed the formation of two isomeric products.<sup>6</sup> The major product was the expected (methyl ketones were formed exclusively in previous zinc chloride isomerizations) 3-ethyl-3-phenyl-2-pentanone with only a small amount of 4-methyl-4-phenyl-3-hexanone being isolated. But treatment of  $\alpha,\alpha$ -dimethylbutyrophenone with zinc chloride gave only 33.5% of the expected 3-methyl-3-phenyl-2-pentanone.<sup>7</sup> And isomerization of the dimethylbutyrophenone with perchloric acid gave only 1% of the 2-pentanone, the major product being 2-methyl-2-phenyl-3-pentanone. The investigators interpreted these results as suggesting that the 3-pentanone was the major product from both reactions but under the more severe conditions imposed by zinc chloride the 3-pentanone isomerized to the 2-pentanone. This was shown to be the case by isomerizing the 2-methyl-2-phenyl-3-pentanone to the 2-pentanone in quantitative yield with zinc chloride at 310°.

Ketone isomerizations were also observed by Zook and coworkers during a study of the Schmidt reaction.<sup>8</sup> They found that 2,2-dimethyl-3-pentanone isomerized to 3,3-dimethyl-2-pentanone under the conditions of the Schmidt reaction as well as in sulfuric acid without the presence of hydrazoic acid. Other ketones isomerized in



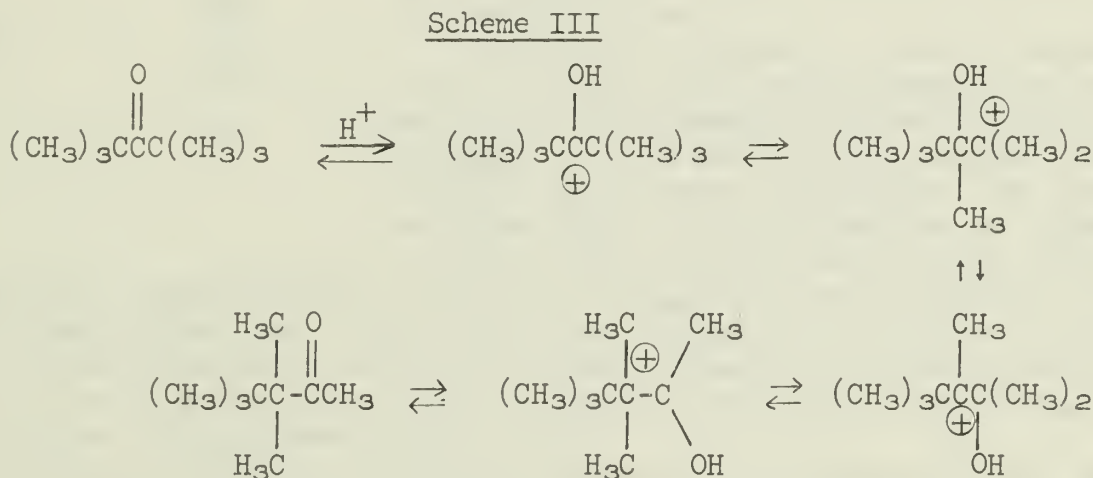


a similar manner and the authors proposed a mechanism involving a protonated epoxide intermediate to explain these results (Scheme II).



Barton and his associates examined the effect of concentrated sulfuric acid on several branched-chain ketones in aromatic solvents. They found that hexamethylacetone and 2,2,4-trimethyl-2-pentanone isomerized in 80% yield to 3,3,4,4-tetramethyl-2-pentanone and 3,3,4-trimethyl-2-pentanone respectively.<sup>9,10</sup> But under the same conditions diisopropyl ketone, diisobutyl ketone and 2,2-dimethyl-3-pentanone did not undergo any change. The authors concluded that in order for rearrangement to occur the carbonyl carbon had to be adjacent to two quaternary carbon atoms or to one quaternary and one ternary carbon atom. They also postulated a mechanism involving oxygen migration but occurring through a 1,2-hydroxyl shift rather than an epoxide intermediate (Scheme III).<sup>9</sup>

To test this hypothesis, Barton and Porter isomerized hexamethylacetone labeled with C-14 in the carbonyl carbon.<sup>10</sup> They found that all of the label remained in the carbonyl carbon after isomerization proving that in this case, an oxygen function migration was not occurring. Probably a mechanism similar to that proposed by Zalesskaya was operative (Scheme I).



One of the few kinetic investigations of ketone isomerizations was conducted by Zook and coworkers.<sup>11</sup> They found that the isomerizations were first-order in the disappearance of reactant and in the particular case of hexamethylacetone,  $\beta$ -cleavage of the product occurred in a consecutive first-order process to give isopropyl methyl ketone.

Table I contains a representative listing of five of the nine ketones studied by Zook with their equilibrium and first-order rate constants. The other four ketones show expected behavior and are not pertinent to the following discussion.

A rationalization for the driving force of the rearrangement is not readily apparent in the data of Table I. Release of internal strain is not an acceptable explanation as the rearranged products are equally or more branched than the reactants and, therefore, contain at least an equivalent amount of internal strain. And relative carbonium ion stabilities are meaningless here because all three ketones



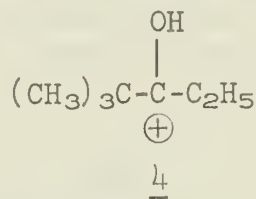
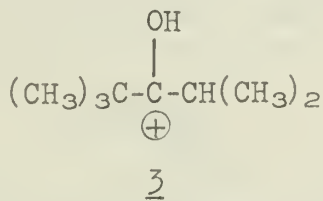
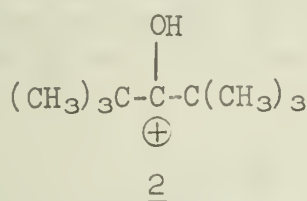
Table I

Isomerization Constants for RCOR'

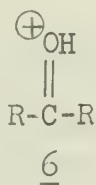
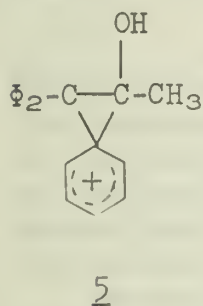
R	R'	% H <sub>2</sub> SO <sub>4</sub>	K	k, sec <sup>-1</sup> x 10 <sup>5</sup>
(CH <sub>3</sub> ) <sub>3</sub> C	(CH <sub>3</sub> ) <sub>3</sub> C	93.7	a	27.3
(CH <sub>3</sub> ) <sub>3</sub> C	(CH <sub>3</sub> ) <sub>2</sub> CH	94.2	6.2	1.8
(CH <sub>3</sub> ) <sub>3</sub> C	C <sub>2</sub> H <sub>5</sub>	93.0	5.5	1.6
Ⓢ <sub>3</sub> C	CH <sub>3</sub>	96.7	-	1500 <sup>1,2</sup>
(CH <sub>3</sub> ) <sub>2</sub> CH	(CH <sub>3</sub> ) <sub>2</sub> CH	95.8	-	0.0

a, Could not be measured.

form essentially the same tertiary ion on migration of a methyl group. The observed trend in rate and equilibrium constants can be explained, however, on the basis of hyperconjugation. Since the three ketones all isomerize to methyl ketones, the products will be stabilized to the same extent by hyperconjugation. But the initial hydroxycarbonium ions 2, 3 and 4, formed by protonation of the reactants, will vary



in the extent of hyperconjugative stabilization. Thus, on this basis, ion 4 should be the most stable of the three ions followed by 3 and then by 2, the least stable of the three carbonium ions. This prediction is reflected in the decreasing rates of isomerization and extent of rearrangement equilibria in Table I as one proceeds from the ketonic precursors of 2 to those of 3 and 4. The extremely facile isomerization of methyl trityl ketone can be explained by the lowering of the transition state energy via the phenonium ion 5.



A plot of the specific rate of isomerization versus sulfuric acid concentration for the isomerization of hexamethylacetone did not give a straight line indicating that protonation of the carbonyl is not rate determining. And another study has shown that the isomerization of hexamethylacetone is first order in the concentration of its conjugate acid, suggesting a mechanism that involves a transition state resembling the conjugate acid.<sup>13</sup> Low temperature nmr studies conducted by Olah and coworkers on protonated ketones have given conclusive evidence for the existence of these carbonium ions although the results demonstrate that the important resonance form is the oxonium ion 6 and not the hydroxycarbonium ion.<sup>14,15</sup>

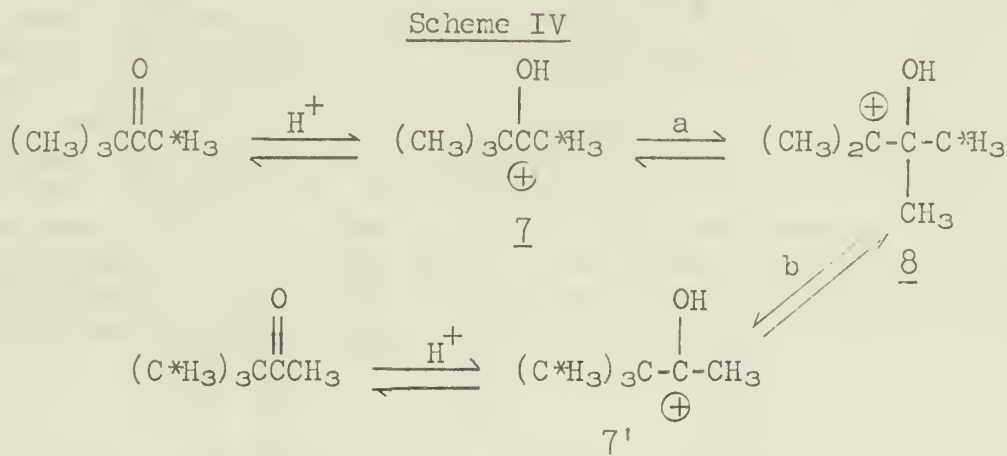
The existence of epoxides in ketone isomerizations (Scheme II) has never been demonstrated although Favorskii postulated their intermediacy as early as 1926.<sup>16</sup> More positive results have been obtained in studies on the closely related pinacol rearrangement. For example, Gebhart and Adams studied the rearrangement of benzopinacol to give benzopinacolone in perchloric acid.<sup>17</sup> The kinetics of the reaction indicated that product formation was occurring through two separate pathways, one involving some type of intermediate and the other a direct rearrangement to product. By stopping the reaction before completion, the authors were able to isolate tetraphenylethylene oxide and this material, on treatment with acid, went on to form benzopinacolone. At 75°, 80% of the reaction proceeded through the epoxide intermediate.

The reversible nature of ketone isomerizations was demonstrated by Fry and coworkers in the isomerization of 3,3-dimethyl-2-butanone-1-<sup>14</sup>C.<sup>18</sup> After sufficiently long reaction times the investigators found that the label was distributed equally

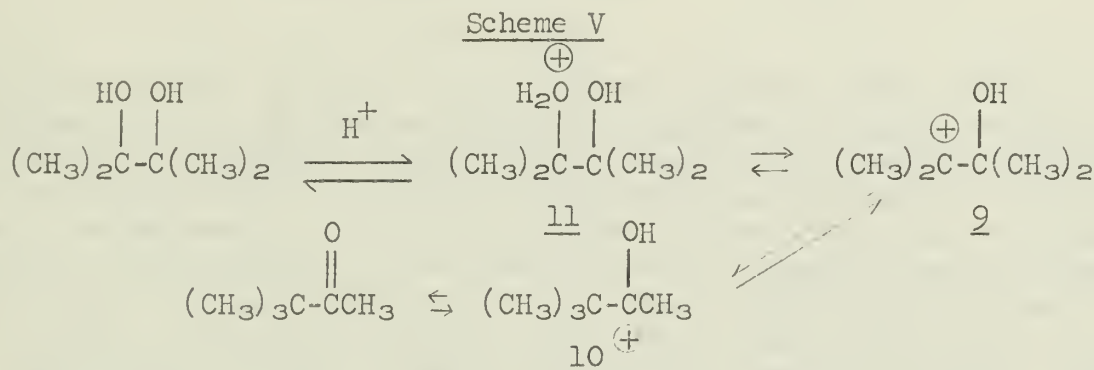




among all four methyl groups. On the basis of Barton's work<sup>10</sup> and Stiles and Mayer's study,<sup>13</sup> Fry concluded that this result could best be interpreted by means of a mechanism that did not involve oxygen migration (Scheme IV).



The reversibility shown in the mechanism is manifest in the total distribution of the label throughout the molecule as described above. On examination of the mechanism for the pinacol rearrangement (Scheme V), it is evident that ions 9 and 10 are identical to 8 and 7 respectively in Scheme IV. Thus, it appears



that both mechanisms proceed through the same two carbonium ion intermediates. This inference led Fry to suggest that the reversibility between 9, 10, and 11 in the pinacol rearrangement could be an equally feasible mechanistic pathway for ketone isomerizations. Although reversible exchange with water has been demonstrated in the pinacol rearrangement using O-18 labeled water,<sup>19</sup> no such process has been shown to occur in the isomerization of ketones.

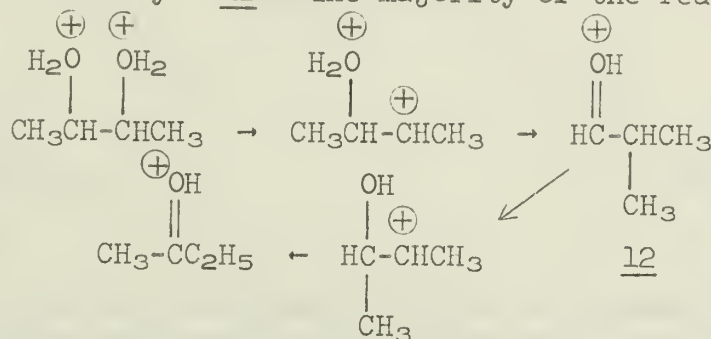
Several Russian investigators have obtained evidence which they interpret as demonstrating that 1,2-shifts in ketone isomerizations are concerted and not stepwise as the preceding mechanism implied.<sup>20,21</sup> The authors conducted hydrogen-deuterium exchange studies on pinacol and pinacolone in deuterated sulfuric acid and interpreted the results assuming that all of the hydrogen atoms on a carbon adjacent to a carbonium ion center will undergo deuterium exchange.<sup>22</sup> Thus, if the rearrangement of pinacol (Scheme V) occurs in a stepwise fashion, both carbonium ions 9 and 10 will result and a total of nine hydrogen atoms will be exchanged. However, if the reaction is concerted, only 10 will be produced with a total of three hydrogens undergoing exchange; no deuterium will be present in the *t*-butyl group. On rearrangement the authors found deuterium residing only in the methyl group and no deuterium in the *t*-butyl group. From this result they concluded that formation of 10 must be a concerted process and that either carbonium ion 9 does not exist or it is so short-lived that it does not undergo exchange.

Extending this argument to the isomerization of pinacolone, the Russian authors felt that steps a and b in Scheme IV ought to be concerted also. When the pinacolone was isomerized in deuteriosulfuric acid, the workers found that more than three hydrogens had exchanged for deuterium in the *t*-butyl group. This result was rationalized by stating that since carbonium ions 7 and 7' are formed in the isomerization, they will undergo exchange. And because of the reversibility of the pinacol rearrangement, ions 7 and 7' will become equilibrated and, thus, allow for complete distribution of deuterium label throughout the molecule. The authors again concluded



that either ion 8 does not exist or it is very short-lived and the isomerization must, therefore, proceed in a concerted manner.

Oxygen-18 exchange studies in the pinacol rearrangement lead to a conclusion opposite to that expressed by the Russian authors.<sup>19</sup> In dilute sulfuric acid pinacol undergoes O<sup>18</sup> exchange with water almost three times as fast as it rearranges, and additional kinetic studies have indicated that the rate determining step is the migration of a methyl group to yield 10 (Scheme V). These observations can be readily explained by invoking the intermediate formation of carbonium ion 9. Olah and coworkers have observed the low temperature nmr spectra of several diprotonated  $\alpha$ -glycols and have found that when these materials were warmed they underwent rapid pinacol rearrangement.<sup>23</sup> Although most of the glycols tested were primary, the one secondary glycol employed gave evidence for a partial stepwise mechanism through the protonated aldehyde 12. The majority of the reaction proceeded via a



rapid hydride shift but the fact that the above mechanism does occur to some extent indicates that tertiary glycols would probably proceed through a stepwise mechanism.

In spite of the apparent contradiction between the deuterium and oxygen-18 exchange studies, the evidence seems to favor a stepwise mechanism for the acid-catalyzed isomerization of ketones. In the case of pinacol, the deuterium exchange studies do not rule out the existence of the intermediate carbonium ions but simply indicate that the reverse reaction is very slow, thus, allowing for no deuterium in the *t*-butyl group. And the results for pinacolone simply demonstrate the reversibility of the isomerization in agreement with Fry's carbon-14 study. However, more investigation is necessary before any definite mechanistic conclusions may be reached. A low temperature nmr study may provide the necessary answers.

The complexity of this problem is further illustrated by another study conducted by Fry and coworkers.<sup>24</sup> They isomerized pinacolone labeled with C<sup>14</sup> in the carbonyl carbon in concentrated sulfuric acid and then cleaved the resulting product to carbon dioxide and *t*-butyl amine. They found that all of the label was contained in the carbon dioxide showing that the oxygen remained on the same carbon atom during the reaction. However, when the ketone was treated with 70% perchloric acid, they found that the label was distributed between the carbon dioxide and the amine in such a manner as to correspond to 38% isomerization via an oxygen function migration.

Several additional studies confirmed that oxygen migrations were operative in certain cases. Fry and Carrick examined the isomerization of triphenylacetophenone labeled with C-14 in the carbonyl carbon.<sup>25</sup> They found that in weakly acidic media (1:1 AlCl<sub>3</sub>/H<sub>2</sub>O in benzene), isomerization through oxygen migration occurred only to an extent of 1.6%, but under more stringent conditions (con. H<sub>2</sub>SO<sub>4</sub> in acetic acid) 46.8% of the isomerization proceeded through oxygen migration. In contrast, diphenylacetophenone showed no detectable isomerization in concentrated sulfuric acid at 0° or in refluxing formic acid.<sup>26</sup> Isomerization of pivalophenone labeled with C-14 in the carbonyl in perchloric acid showed 40% reaction through oxygen migration<sup>27</sup> and treatment of C-14 labeled (in the carbonyl group) 2,2-dimethylpropionophenone with perchloric acid showed the same type of migration occurring to an extent of 34%.<sup>28</sup>

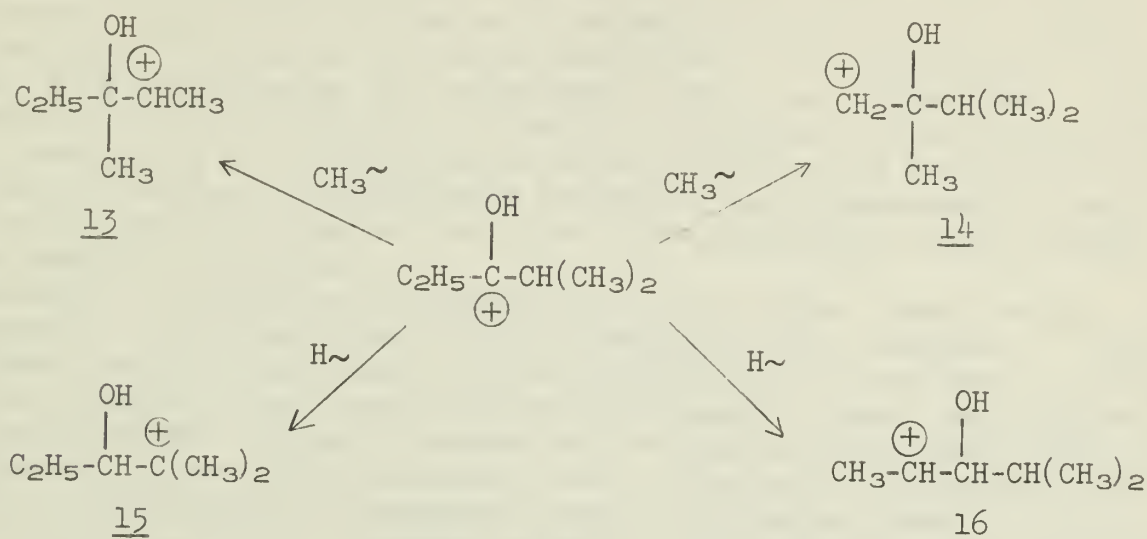
Isomerization of less highly branched ketones has been accomplished by Fry and coworkers using a solid supported phosphoric acid catalyst.<sup>29</sup> Ketones readily rearrange on this catalyst to give products that can be rationalized on the basis of isomerization via the most stable carbonium ion.





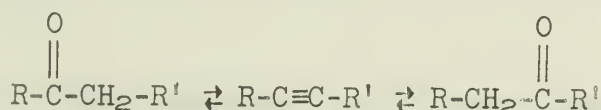


For example, isomerization of 2-methyl-3-pentanone with the catalyst at 300° gave only 3-methyl-2-pentanone and none of the other isomer, 4-methyl-2-pentanone.<sup>29</sup> This result may be accounted for by examination of the various carbonium ions that might arise from the conjugate acid. A methyl shift from the conjugate acid would



produce either the secondary carbonium ion 13 or the primary ion 14 and a hydride shift from the conjugate acid would yield either ion 15 or 16. The two ions 13 and 15 would result in the formation of the observed product, 3-methyl-2-pentanone, while ions 14 and 16 would give 4-methyl-2-pentanone. As ion 13 would be expected to be more stable than 14, and 15 more stable than 16, formation of 3-methyl-2-pentanone is favored. Similar reasoning accounts for the products obtained in the other isomerizations conducted by Fry and coworkers.

Although no mechanistic conclusions could be obtained from the above results, Fry suggested that reversible alkyne formation was an equally plausible isomerization pathway for ketones containing at least two hydrogen atoms adjacent to the carbonyl group.<sup>29</sup> Hydration of alkynes is known to give ketones and when a mixture of water



and 2-pentyne was passed over the catalyst at 300°, 2- and 3-pentanone were obtained in yields of 43.2% and 40.5% respectively.<sup>29</sup>

If the isomerization of 2-methyl-3-pentanone was to proceed via alkyne formation, then the intermediate alkyne produced would be 4-methyl-2-pentyne. When this material was passed over the catalyst with water, the authors isolated 4-methyl-2-pentanone in 47% yield, 2-methyl-3-pentanone in 12.5% yield and 3-methyl-2-pentanone in 8.8% yield. But as shown earlier, the major product from the isomerization of 2-methyl-3-pentanone was 3-methyl-2-pentanone and not 4-methyl-2-pentanone as the hydration experiment indicates. Thus, alkyne formation is not operative in this case. The fact that no alkynes could be detected in any of the isomerizations run by Fry lends credence to the view that this mechanism is not operative in any ketone isomerization.

The authors also attempted to isomerize several alicyclic ketones with the phosphoric acid catalyst but they found that the major process was not isomerization but dehydration followed by dehydrogenation to give aromatic hydrocarbons. Thus, 2,6-dimethylcyclohexanone at 300° gave only a trace of methyl 2-methylcyclopentyl ketone along with 58% *m*-xylene and 19.5% *o*-xylene.<sup>29</sup> Similarly, cyclohexanone gave benzene at 300° and 2-methylcyclohexanone formed toluene with only a trace of methyl cyclopentyl ketone.

#### STRAIGHT-CHAIN ALIPHATIC KETONES

Prior to 1960 it was believed that in order for a ketone to isomerize a tertiary carbonium ion had to result from the migration of a substituent on the conjugate acid.



This idea was disproved, however, when Fry observed the isomerization of diisopropyl ketone and 2-pentanone to 3,4-dimethyl-2-pentanone and 3-pentanone respectively.<sup>30</sup> These transformations were carried out in perchloric acid and large amounts of tar resulted.

More recently, Fry and coworkers have found that straight-chain aliphatic ketones isomerize extensively on the solid supported phosphoric acid catalyst mentioned earlier.<sup>29</sup> Using this catalyst they were able to interconvert 2- and 3-pentanone, 2- and 3-hexanone and 3-heptanone with 2- and 4-heptanone. Examination of this latter interconversion for a 1,3-shift in addition to the 1,2-shift was futile; it seems to be a negligible process in straight-chain ketones. The authors were also able to achieve an equilibrium between 2- and 3-pentanone although this was not possible with any other ketone tried. The equilibrium ratio was 68% 2-pentanone and 31% 3-pentanone.

In an effort to determine the mechanism of this latter isomerization, Fry and Corkern isomerized 3-pentanone-3-C<sup>14</sup> on the phosphoric acid catalyst.<sup>31</sup> The resulting ketonic products were then oxidized with perbenzoic acid and the esters converted to acetanilide and propyl 3,5-dinitrobenzoate. These materials were then analyzed for their carbon-14 content and the authors found that 99% of the label was present in the dinitrobenzoate ester. This result demonstrates that the conversion of 3-pentanone to 2-pentanone proceeds through an oxygen function migration.

Which of the four kinds of oxygen migration is involved in these isomerizations cannot be determined from the preceding results. Fry has already presented evidence that reversible alkyne formation is an unlikely process and an unpublished study of the effect of water activity (at high acid concentrations) on the rate of oxygen function rearrangement in pinacolone seems to eliminate reversible pinacol formation for that case at least.<sup>29</sup> Thus, the most plausible intermediates for oxygen migration appear to be the 1,2-hydroxyl shift or the protonated epoxide.

Some ketones under certain conditions do not give isomerization but instead undergo disproportionation.<sup>32</sup> Thus, when 2-butanone is heated with 70% perchloric acid, the products that are obtained include acetone, 2- and 3-pentanone and 3-hexanone. Similar behavior has been observed with 3-pentanone, acetone and 4-heptanone. An aldol condensation-carbonium ion rearrangement mechanism has been proposed for this process.

## CONCLUSION

The complexity of ketone isomerizations is made apparent by the variation of mechanism depending upon the reaction conditions and the structure of the particular ketone employed. Aromatic and branched-chain aliphatic ketones seem to favor a concerted or stepwise series of 1,2-aryl, alkyl or hydride shifts, although in some cases the mechanism involves a combination of one of these shifts with an oxygen function migration. Less highly branched and straight-chain aliphatic ketones favor oxygen function migration and the most likely intermediates appear to be the 1,2-hydroxyl shift or the protonated epoxide. Trends in rate and equilibrium constants may be rationalized on the basis of hyperconjugation and in most situations, reaction pathways may be predicted on the basis of isomerization via the most stable carbonium ion.

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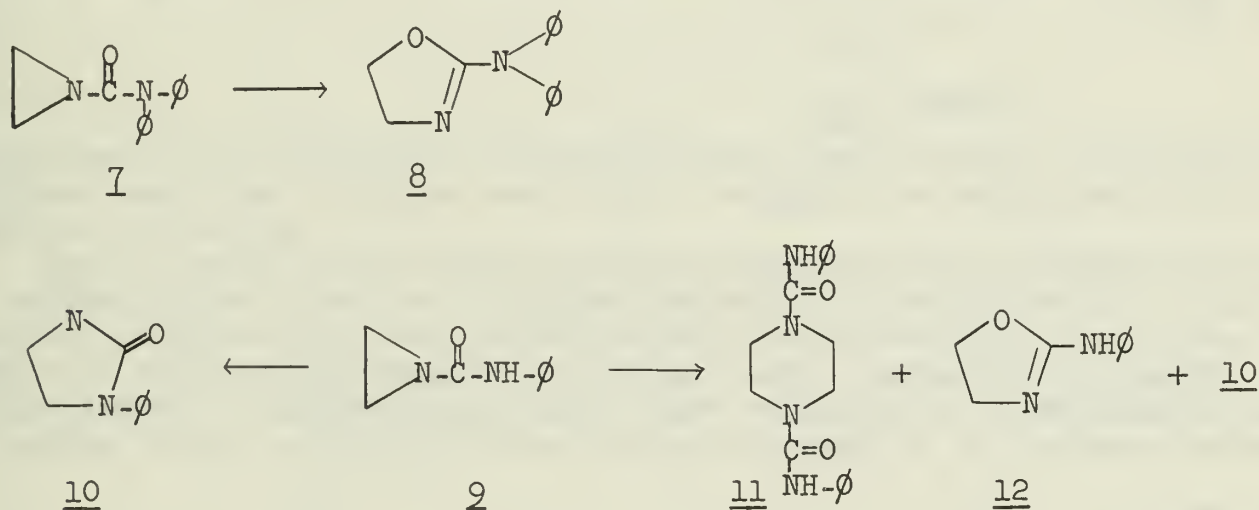




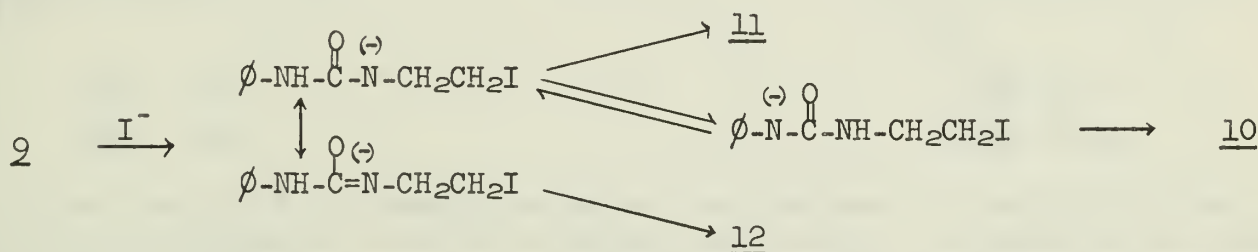
benzamide compounds, which have been found to readily cyclize to oxazolines.<sup>4</sup> Although conclusive evidence has not been found to discount the first mechanism completely, the intermediate benzamido ion pathway will be predominantly employed in this seminar to interpret these nucleophile-catalyzed rearrangements.

The rearrangement of 1-arylaziridines by the action of sodium iodide in acetone seems to be a general method for the preparation of 2-aryl-2-oxazolines. Other aroyl-derivatives isomerized in good yield are 1-*p*-chlorobenzoyl-, 1-*p*-ethoxybenzoyl-, and 1-(3,5-dinitrobenzoyl)aziridine<sup>2</sup> and 1-*p*-nitrobenzoyl-2-ethylaziridine.<sup>5</sup>

Heine and coworkers<sup>5</sup> found that while *N,N*-diphenyl-1-aziridinecarboxamide (7) was readily isomerized to the expected oxazoline (8) by sodium iodide, the results from treatment of 1-aziridinecarboxanilide (9) with this catalyst in acetone were less definitive. The use of a large excess of sodium iodide and a small quantity of acetone effected the isomerization of 9 to 1-phenylimidazolidin-2-one (10) in 85% yield. Using smaller amounts of the iodide catalyst in larger quantities of acetone

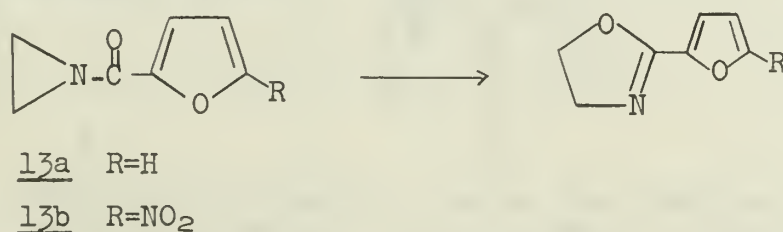


Scheme I



gave predominantly the dimer, *N,N'*-bis(phenylcarbamoyl)piperazine (11), together with some 10 and 2-anilino-2-oxazoline (12). A mechanistic pathway was presented (Scheme I) to account for the various products, although no rationale was suggested for the actual effect of the different sodium iodide and acetone quantities.

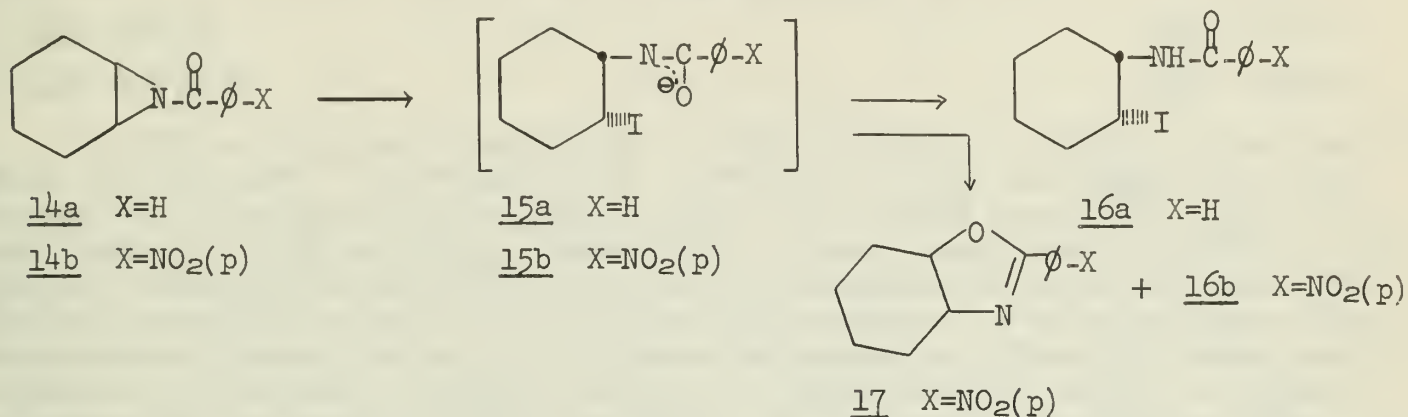
Lidaks and Hillers<sup>6</sup> observed normal rearrangements when 1-(2-furanoyl)aziridine (13a) and 1-(5-nitro-2-furanoyl)aziridine (13b) were treated with sodium iodide-acetone; they ascribed the reduced ease of reaction of the substituted furanoyl derivative to the reduced electron supply at the reactive site. This explanation



would support the second mechanism for nucleophile-catalyzed rearrangement involving an intermediate *N*-( $\beta$ -iodoethyl)benzamido ion which undergoes facile cyclization to the oxazoline. Thus, the facility of the aroylaziridine to isomerize should correspond to the transmission of the electronic effects in conjugation with the *N*-carbonyl moiety.

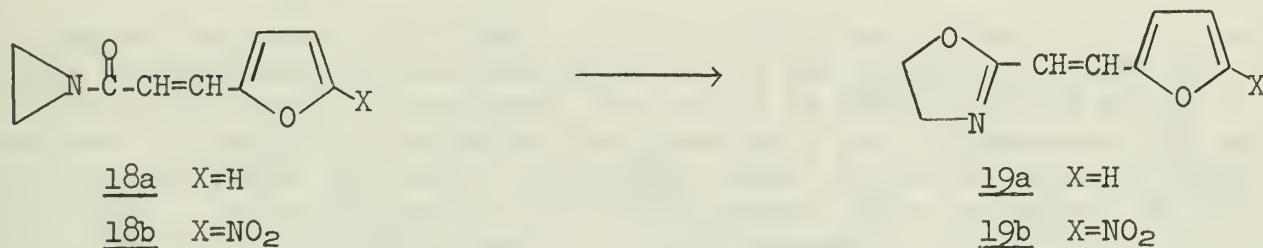


In support of this conclusion, Fanta and Walsh<sup>7</sup> reported that N-benzoyl-7-azabicyclo[4.1.0]heptane (14a) rearranged to trans-1-iodo-2-benzamidocyclohexane (15a) upon treatment with an acetone solution of sodium iodide, while under the same reaction conditions, the *p*-nitrobenzoyl derivative 14b yielded predominantly the normal oxazoline 17 plus some of the iodo-amide compound. An explanation for this difference in reactivity might suggest that the more strongly basic intermediate ion

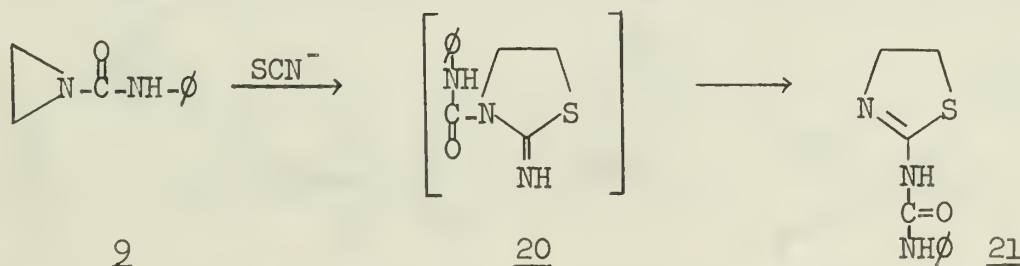


15a preferentially abstracts a proton from the solvent system to form the iodo-amide; the less basic, and therefore more stable ion 15b may be sufficiently long-lived to undergo cyclization.

Several other workers have recently noted nucleophilic-catalyzed rearrangements of acylaziridines; Susaki and Yoshioka<sup>8</sup> reported the isomerization of 1-( $\beta$ -furyl-acryloyl)aziridine (18a) and its 5-nitrofuryl derivative 18b to oxazolines 19a and 19b to be affected by treatment with sodium iodide, potassium thiocyanate, or tributylamine. 1-Carbethoxyaziridine,<sup>9</sup> upon refluxing in an acetonitrile solution of sodium iodide, was found to give 2-ethoxy-2-oxazoline as the major product.



As has been noted in previous examples, rearrangement of acylaziridines can be catalyzed by nucleophiles other than sodium iodide with no changes in the observed products. An interesting reaction in which this trend is not operative was reported by Najer, *et al.*<sup>10</sup> Independently from Heine,<sup>5</sup> they observed the isomerization of 1-aziridinecarboxanilide (9) to 1-phenylimidazolidin-2-one (10), catalyzed by sodium iodide in acetone solution. The same aziridine, however, upon reflux with potassium thiocyanate in acetone, yielded an addition product, 2-(N<sup>1</sup>-phenylureido)-2-thiazoline (21) which could be visualized as proceeding through an intermediate such as 20.

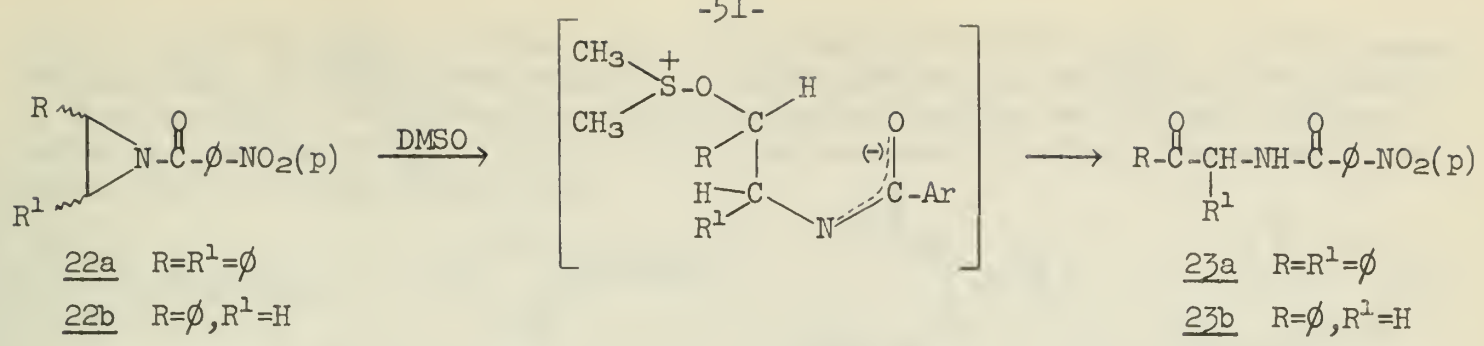


Heine and Newton<sup>11</sup> have recently reported the reactions of substituted aroyl-aziridines with dimethyl sulfoxide in which dimethyl sulfoxide acts as a nucleophile similar to iodide. The reaction products, however, are derivatives of N-phenacyl-benzamides. Upon heating to 115° in dimethyl sulfoxide, *cis*- and *trans*-1-(*p*-nitrobenzoyl)-2,3-diphenylaziridine (22a) rearranged to N-desyl-*p*-nitrobenzamide (23a) in 8% and 52% yields, respectively, while similar treatment of the 2-phenyl derivative 22b resulted in good yields of N-phenacyl-*p*-nitrobenzamide (23b).

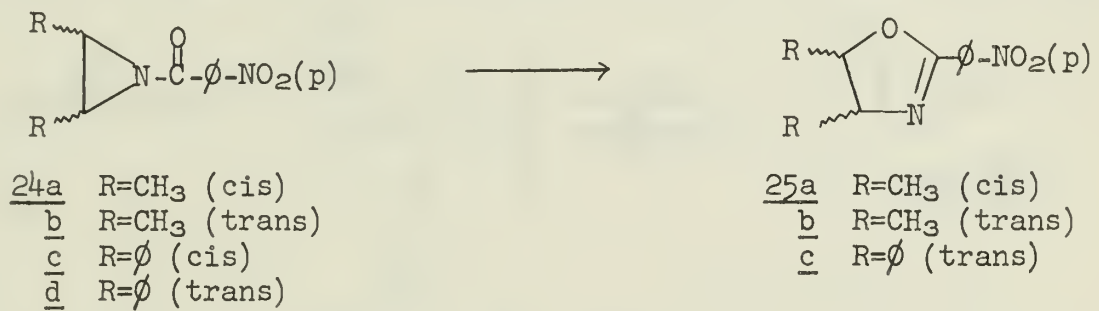




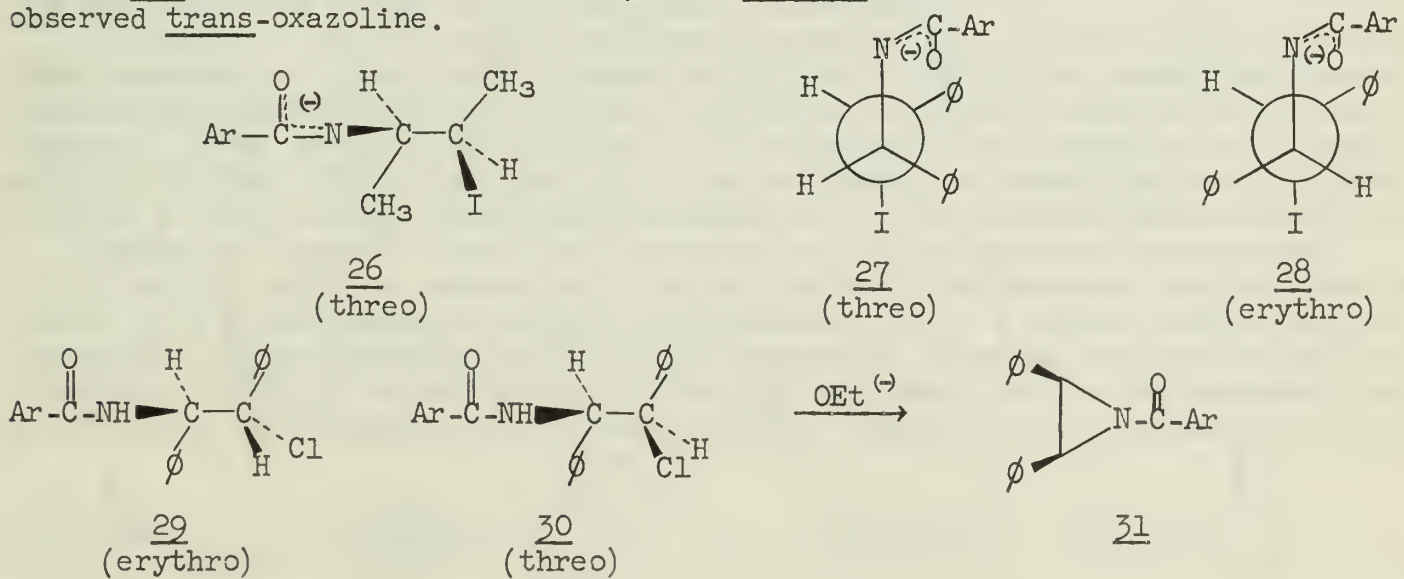




In studying the stereospecificity of these nucleophile-catalyzed rearrangements, Heine and coworkers<sup>12</sup> investigated the conversions of cis- and trans-1-(p-nitrobenzoyl)-2,3-dimethylaziridine (24a,b) to the substituted oxazolines 25a,b, which were found to be cis and trans, respectively. These results are in accord with the proposed mechanism involving the attack of a nucleophile on an aziridinyl carbon (Walden inversion) to form the N-( $\beta$ -iodoethyl)benzamido ion which undergoes internal O-alkylation (Walden inversion) to produce the oxazoline. Thus, 24a would give a benzamido intermediate of threo configuration 26 which would cyclize to cis-2-p-nitrophenyl-4,5-dimethyl-2-oxazoline (25a). In the case of the cis and trans diphenyl derivatives 24c,d, both compounds were found to form the trans-oxazoline 25c.



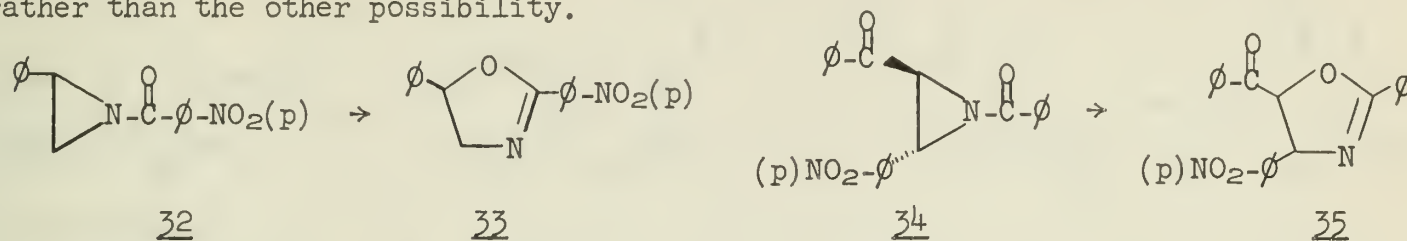
Model studies indicated considerable steric interaction of the two phenyl groups in the threo intermediate 27 which did not exist in the erythro conformer 28. Further evidence for this steric interference was gained by observing that alkaline ethanolysis of threo-N-(1,2-diphenyl-2-chloroethyl)-p-nitrobenzamide (30) produced only the cis-aziridine 31, while the erythro isomer 29 formed only the trans-oxazoline 25c. In explaining this apparent anomaly, Heine suggested that the cis-aziridine may be in equilibrium with the threo-benzamido ion, which is sterically prevented from forming the cis-oxazoline. The threo ion is converted to erythro by iodide via the Finkelstein reaction; this erythro ion can then cyclize to give the observed trans-oxazoline.



The mechanism of these rearrangements suggests that the position of initial attack by the nucleophile on one of the aziridinyl carbons should be influenced by both steric and electronic factors. In the examples discussed previously, suitable substituents were not used to identify the dominant influence. Heine and Kaplan<sup>13</sup> resolved this problem by investigating the rearrangements of 1-p-nitrobenzoyl-2-

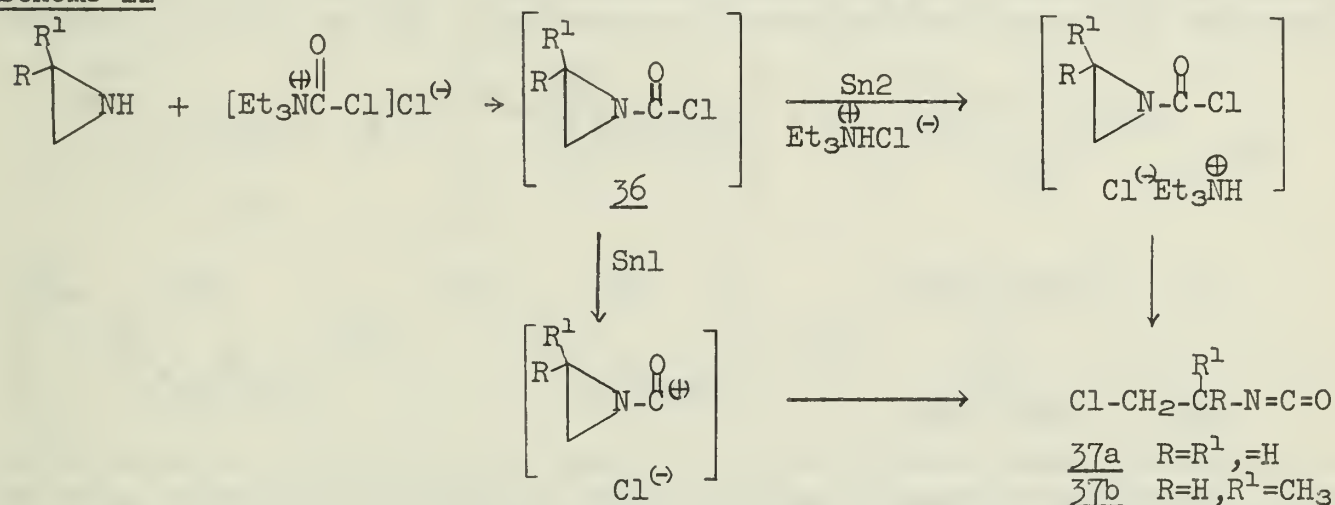


phenyl- (32) and trans-1,2-dibenzoyl-3-p-nitrophenylaziridine (34). In both cases the products, 33 and 35, respectively, suggest that steric factors are not dominant in ring opening; the nucleophile attacks the more positive and the more hindered carbon in the case of 32 to form the N-(2-iodo-2-phenylethyl)-p-nitrobenzamido ion rather than the other possibility.



Recently, Johnson<sup>14</sup> has postulated the rearrangement of an acylaziridine as an intermediate in the attempted preparation of 1-aziridinecarbonyl chloride 36. The reaction of ethylenimine and phosgene in triethylamine gave, instead of the expected product, 2-chloroethyl isocyanate (37a). 1-Aziridinecarbonyl chloride was proposed as an intermediate which could rearrange to the isocyanate by either  $S_N1$  or  $S_N2$  pathways as shown in Scheme II. The formation of 2-chloropropyl isocyanate (10%) and 1-chloro-2-propyl isocyanate (33%) from similar treatment of 2-methylaziridine was

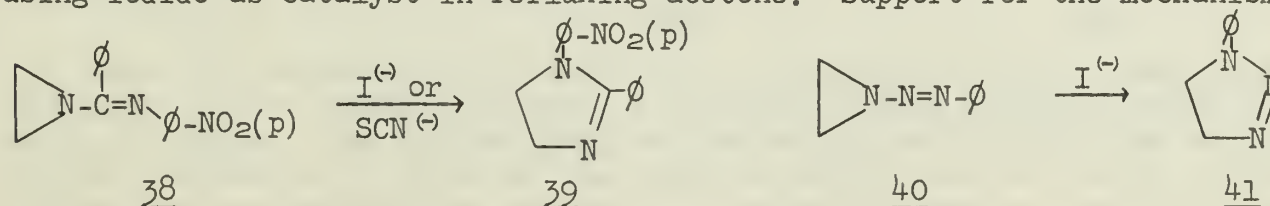
Scheme II



postulated to arise predominantly by a  $S_N2$  pathway. The products resulting from 2,2-dimethylaziridine were accounted for by the  $S_N1$  route in which the carbamoyl cation partitioned itself between reaction with a chloride ion to give the major product 37b and loss of a proton to give methallyl isocyanate.

In addition to nucleophile-catalyzed isomerizations of acyl- and aroylaziridines, rearrangements of other 1-substituted aziridines in which the substituent has an  $\alpha$ -unsaturated moiety other than carbonyl are known to produce novel heterocyclic systems. These carbonyl derivatives would be expected to isomerize in a manner similar to their oxygen analogs; e.g. 1-aziridinethiocarboxanilide was reported to undergo a normal iodide-catalyzed rearrangement to the 2-substituted-2-thiazoline.<sup>5</sup>

Heine and Bender<sup>15</sup> found that treatment of N-(p-nitrophenyl)benzimidoylaziridine (38) with an acetone solution of iodide or thiocyanate ions afforded good yields of 1-p-nitrophenyl-2-phenyl-2-imidazoline (39). A general method for the preparation of monosubstituted  $\Delta^2$ -1,2,3-triazolines starting from azo-aziridines was reported in 1962;<sup>16</sup> 1-phenylazoaziridine (40) underwent facile rearrangement to 41 using iodide as catalyst in refluxing acetone. Support for the mechanism involving



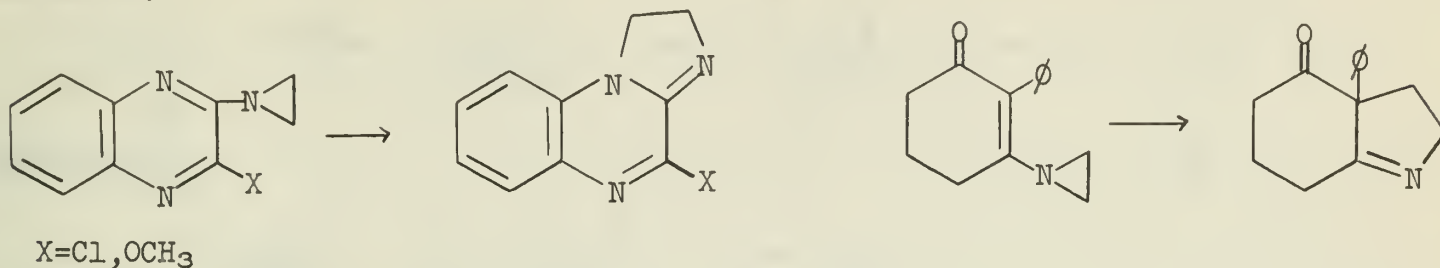
initial attack by iodide was given by the fact that electron-withdrawing groups attached to the aryl group seemed to facilitate the isomerization. In contrast to the 1-phenylazo compound, 1-(p-nitrophenylazo)aziridine rearranged at room temperature





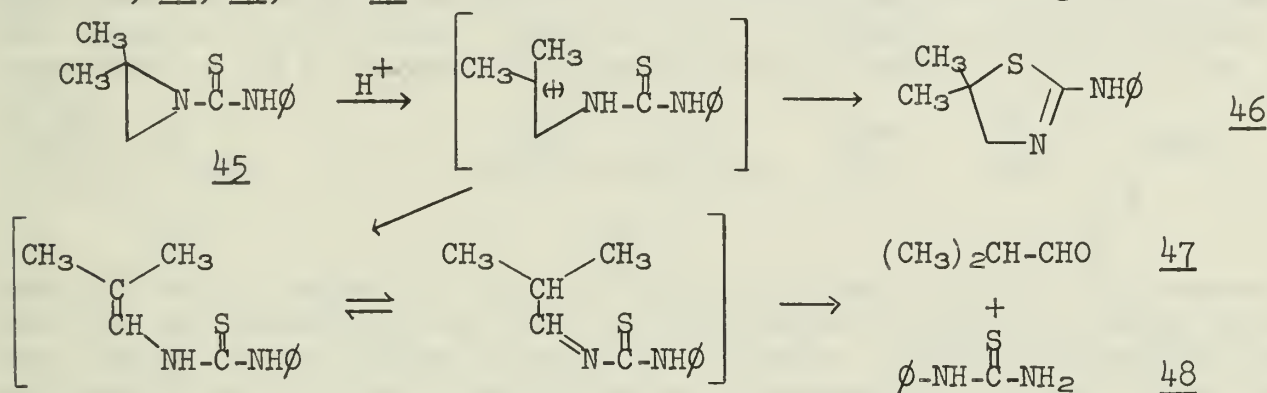


in 15-20 minutes; this suggests that ring opening by iodide is rate determining. Several other rearrangements leading to novel heterocycles are shown below;<sup>17,18</sup> all of these reactions may be rationalized by the proposed benzamido-intermediate mechanism.

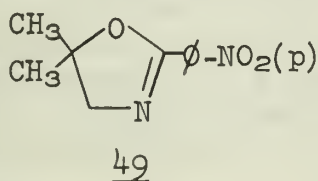


## ACID-CATALYZED REARRANGEMENTS

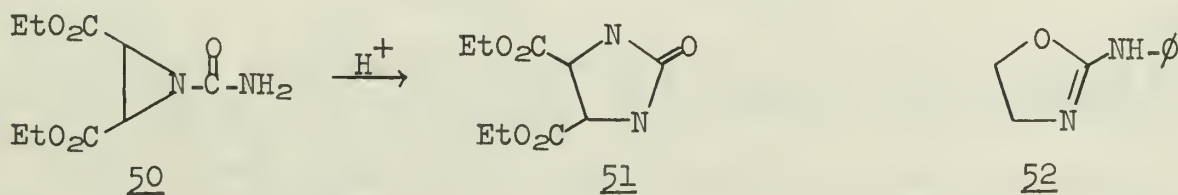
The earliest reported acid-catalyzed rearrangement of 1-acylaziridines was published by Gabriel and Stelzner<sup>19</sup> in 1895; they found that heating 1-aziridine-thiocarboxanilide (which they thought was N-phenyl-N<sup>1</sup>-vinylthiourea) in hydrochloric acid gave 2-anilino-2-thiazoline in 90% yield.<sup>20</sup> Deutsch and Fanta,<sup>20</sup> after studying the reaction of 1-(2,2-dimethylaziridine)thiocarboxanilide (45) with concentrated hydrochloric acid, proposed the indicated mechanism to account for the three observed products, 46, 47, and 48. Protonation of the aziridine nitrogen or thiocarbonyl



sulfur atom is followed by ring opening to give the more stable carbonium ion, which may then undergo ring closure to produce various 5-membered heterocyclic systems or may react in some other manner appropriate for carbonium ions. The acid-catalyzed isomerization of 1-(p-nitrobenzoyl)-2,2-dimethylaziridine, analogously, gives the 2-p-nitrophenyl-5,5-dimethyloxazoline 49 in excellent yield (which is in contrast with the iodide-catalyzed reaction yielding the 4,4-dimethyl oxazoline 4).



The isomerization of two other 1-carbonylaziridines by acid catalysis has also been reported.<sup>21</sup> When heated with dilute hydrochloric acid, 1-carbamyl-2,3-diethoxycarbonylaziridine (50) rearranged into 51, while 1-aziridinecarboxanilide was isomerized in refluxing ethyl acetate-picric acid solution into the expected oxazoline 52.

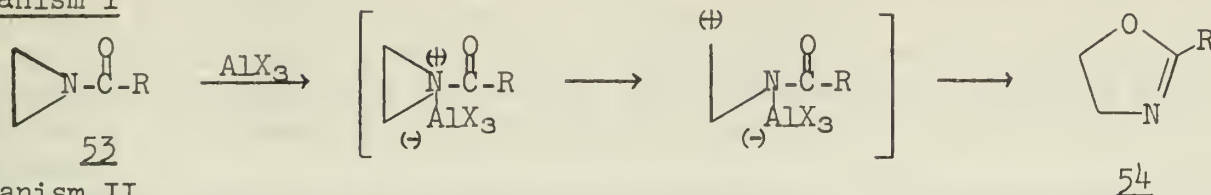


Heine and Proctor<sup>22</sup> also found that 1-arylaziridines are isomerized to oxazolines by the catalytic action of aluminum halides probably acting as Lewis acids in heptane. The authors proposed two mechanisms by which the reaction might proceed. Mechanism I, in which the aluminum halide induces opening of the aziridine ring to give an intermediate carbonium ion which cyclizes to the oxazolinium ion, was not considered to be favorable; a solvent of low dielectric constant, such as heptane, would not favor the generation either of charge in the transition state or even of an intermediate with charge separation. Mechanism II was considered more likely, in

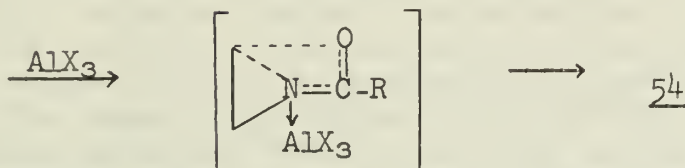


which bond-switching in an aziridine-aluminum halide complex leads to the observed oxazoline.

#### Mechanism I

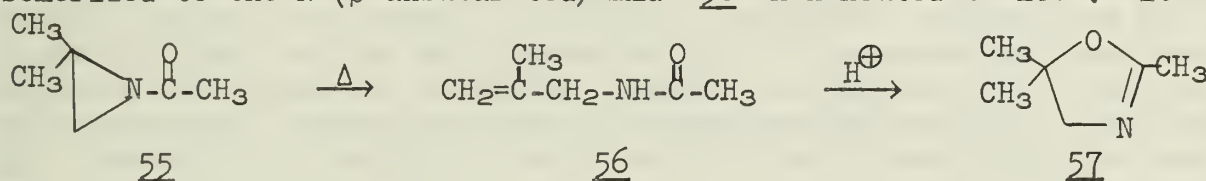


#### Mechanism II



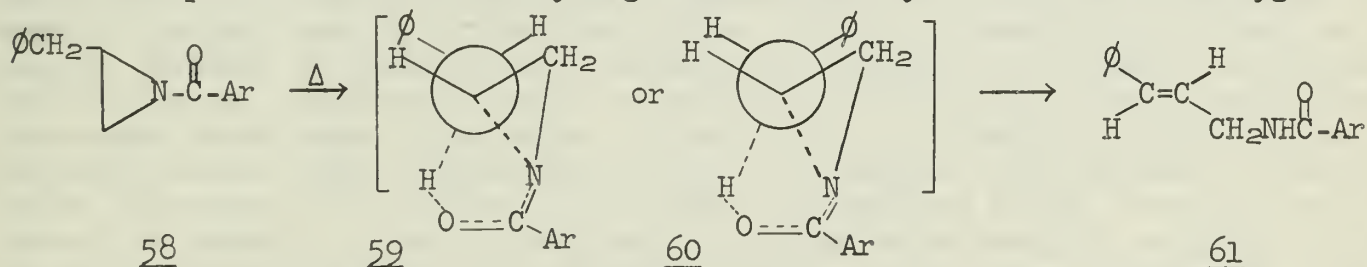
### THERMAL REARRANGEMENTS

Rearrangements of 1-acylaziridines by pyrolysis generally give products different from those obtained from either acid- or nucleophile-catalyzed reactions. Although unsubstituted derivatives, such as 1-benzoylaziridine, are thermally converted to oxazolines, more characteristic is the formation of unsaturated amides from 1-acylaziridines with alkyl substituents. Fanta and Deutsch,<sup>23</sup> in initial observations of this pyrolytic ring opening, reported that 2,2-dimethyl-1-acetylaziridine (55) isomerized to the N-( $\beta$ -unsaturated) amide 56 when heated to 160°. It was also noted



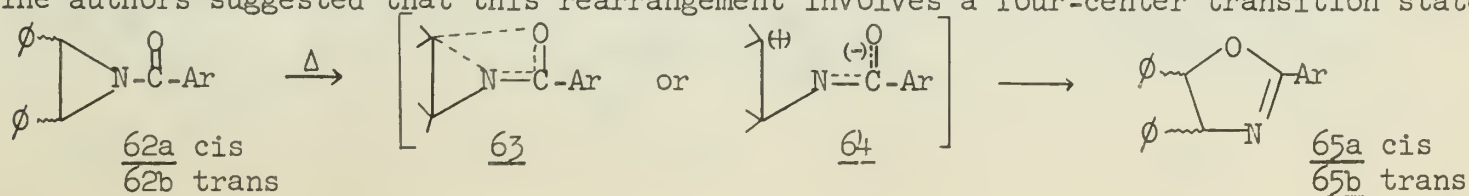
that mild acid treatment of the product 56 resulted in facile rearrangement to the oxazoline 57, suggesting that the initial ring opening must be purely pyrolytic and very similar to the Chugaev reaction of xanthates. After finding that 2-methyl-1-acetylaziridine would not undergo thermal rearrangement, it was further proposed that the additional methyl group satisfied a steric requirement for a sufficiently bulky group to force the participating alkyl moiety close to the acyl oxygen.

In cases in which the rearrangement products are either unsaturated amides or oxazolines, a high degree of stereospecificity has been observed. The thermal rearrangement of 2-benzyl-1-(*p*-nitrobenzoyl)aziridine (58) has been reported to yield only N-*trans*-cinnamyl-*p*-nitrobenzamide (61), suggesting an intramolecular, concerted, and stereospecific transfer of hydrogen from the alkyl substituent to oxygen.<sup>24</sup> Of



the two possible six-membered transition states 59 and 60, the *trans* product seems to arise from the one in which the bulky phenyl group is not unfavorably eclipsed with the methylene group of the aziridine ring.

Whereas it was shown that the iodide-catalyzed isomerization of either *cis*- or *trans*-2,3-diphenylaroylaziridines gave only the *trans* oxazoline, Heine and Kaplan<sup>13</sup> recently reported a stereospecific thermal conversion of *cis*- and *trans*-2,3-diphenyl-1-(*p*-nitrobenzoyl)aziridine (62a,b) into the respective *cis* and *trans* oxazoline 65a,b. The authors suggested that this rearrangement involves a four-center transition state





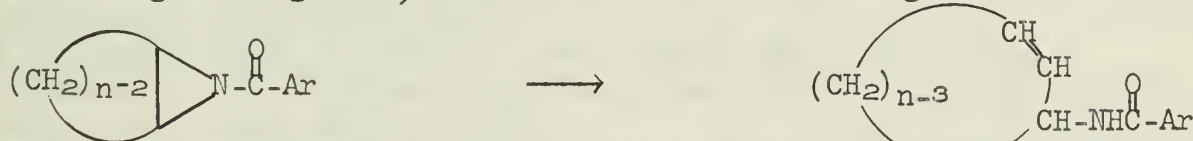




63 or short-lived tight ion pair 64 which collapses to the oxazoline before racemization. In either case attack by the acyl oxygen must occur on the same face of carbon at which the carbon-nitrogen bond is broken. An indication that carbon-nitrogen bond breaking in the aziridine ring is rate determining and occurs prior to carbon-oxygen bond formation is given by the reduced rate of isomerization of cis-2,3-diphenyl-1-benzoylaziridine. Additional derivatives with other electron-donating and electron-withdrawing substituents have not, however, been prepared to fully substantiate this conclusion.

A kinetic study of the thermal rearrangement of 1-(*p*-nitrobenzoyl)-2,2-dimethylaziridine (3) by Fanta and Kathan<sup>25</sup> indicates that this pyrolytic elimination is first order at 72, 86, and 101°. The reaction was monitored by observing the appearance of the N-H band of the product, N-( $\beta$ -methallyl)-1-*p*-nitrobenzamide, at 3370 cm<sup>-1</sup>. The calculation of an entropy of activation (at 86°) of  $-10.4 \pm 1.9$  e.u. is in accord with a highly ordered transition state as proposed in the suggested mechanism.

An interesting study on the effect of ring size in the thermal rearrangement of fused, bicyclic aroylaziridines as represented by 68 has been reported in a series of papers by Fanta, et. al.<sup>7,26-28</sup> It was observed that the attempted preparation of N-benzoylcyclodecenimine (68a, n=10) and N-benzoylcyclooctenimine (68b, n=8) gave directly the isomeric, unsaturated amides 69a,b. In these cases the benzoylaziridines apparently were formed and rearranged very rapidly below 80°. The cyclohexenimine derivative 68c (n=6), however, was found to be completely stable at 150°, and complete rearrangement required heating at 200-210°. It was further observed that when 6-benzoyl-3-oxa-6-azabicyclo[3.1.0]hexane (73), the next lower analog in this bicyclic series, was heated to 235-250°, the product isolated was the fused oxazoline in 33% yield and not the anticipated amide. In interpreting these results, the authors suggested that there is considerably greater strain associated with the attainment of the six-membered transition state in going from 68a and 68b to the azabicycloheptane 68c. Extending the argument, the transition state leading to the unsaturated amide is

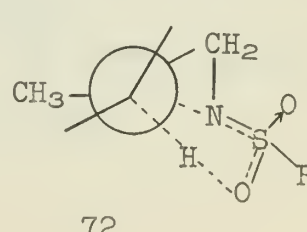
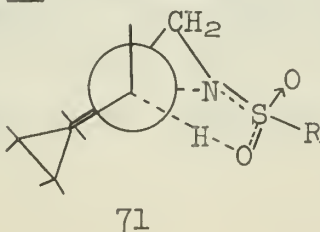
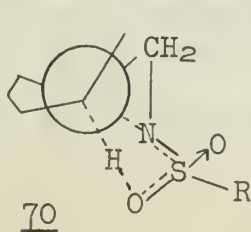


68a, n=10; b, n=8; c, n=6

69a, n=10; b, n=8; c, n=6

so severely hindered in the bicyclohexane 73 that an alternate path to oxazoline formation predominates.

A study was recently carried out to determine the effect on these pyrolytic rearrangements of the inclusion of the aziridine ring in a spiro skeleton with a carbocyclic ring.<sup>29,30</sup> A distinct ring size effect was found in comparing the behavior of the *p*-nitrobenzenesulfonyl derivatives of 1-azaspiro[2.4]heptane, 1-azaspiro[2.5]octane, and 2,2-dimethylaziridine. While the azaspirooctane derivative was readily prepared and isomerized by refluxing in toluene for 16 hours, azaspiroheptane did not form an isolable derivative with the sulfonyl chloride but gave directly the rearranged unsaturated sulfonamide. In addition, the dimethylaziridine derivative required an even higher temperature (150°) to isomerize. The different reactivities can be interpreted by considering the Newman projections of the reactants and proposed transition states. If the rearrangement is a concerted reaction requiring coplanarity of the participating atoms in a six-membered ring, projection formulas 70, 71, and 72 should be considered. It is apparent from these projections or from three-dimensional models that little additional strain is involved in going from the ground state azaspiroheptane to 70; however, for the azaspirooctane derivative, coplanarity requires a shift from the favorable chair conformation of the cyclohexyl group to a comparatively strained twisted conformation in 71. The stronger reaction conditions required for







the dimethylaziridine are attributed to a comparatively large entropy effect associated with the attainment of 72, which greatly constrains the rotational degrees of freedom of the system.

A novel thermal rearrangement of trans-1,2-dibenzoyl-3-(p-nitrophenyl)aziridine to give  $\alpha$ -benzamido-p-nitrobenzalacetophenone has been reported by Heine and Kaplan,<sup>13</sup> who attribute the isomerization to the acidity of the aziridinyll hydrogen adjacent to the benzoyl moiety. A reaction scheme involving transfer of the acidic proton to the aroyl oxygen with or without concurrent breaking of the carbon-nitrogen bond was suggested, as well as the possibility of an ion pair intermediate with direct transfer of the proton to nitrogen.

## CONCLUSION

It has been found that the isomerizations of suitably substituted aziridines, such as 3, are of three general classes: (1) nucleophile-catalyzed rearrangement to give 4-substituted-2-oxazolines; (2) acid-catalyzed rearrangement which yields predominantly 5-substituted-2-oxazolines; and (3) pyrolytic isomerization which gives unsaturated amides. As has been shown, rearrangements of these types are often useful in the synthesis of novel heterocyclic systems.

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PHOTOCHEMISTRY OF AROMATIC NITRO COMPOUNDS

Reported by Craig Marken

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The attention given to the photochemistry of aromatic nitro compounds in the past several years has led to fresh knowledge concerning their excited states. The excited state of aromatic nitro compounds responsible for much of their photochemical behavior is the  $n, \pi^*$  triplet which can lead to hydrogen abstractions in photoreductions and to the possibility of photocycloaddition reactions. In some cases the  $\pi, \pi^*$  triplet is responsible for the observed photochemistry. It is the purpose of this seminar to present some aspects of the basic reactions of the excited states of nitro aromatic compounds and to discuss some of the structural factors influencing their reactivity. It is of interest to note that there are some similarities between the reactions of the excited states of aromatic nitro compounds and those of aromatic aldehydes and ketones.<sup>1</sup>

NITROBENZENE

The electronic spectrum of nitrobenzene in the ultraviolet and visible regions<sup>2</sup> consists of four bands between 200 and 400  $m\mu$ . The bands near 200, 250 and 290  $m\mu$ , with the 250  $m\mu$  band the most intense, are  $\pi, \pi^*$  transitions; they shift to longer wavelength upon increasing solvent polarity. The band at 250  $m\mu$  was described by Nagakura and co-workers<sup>3</sup> as an absorption of an intramolecular charge-transfer complex. The absorption at 330  $m\mu$  results from a  $n, \pi^*$  transition of the nonbonding orbital of the nitro group, and shifts to shorter wavelength upon increasing the hydrogen bonding capabilities of the solvent.

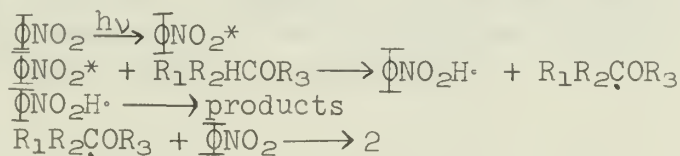
By analogy to the photochemistry of benzophenone, the  $n, \pi^*$  transition of nitrobenzene should facilitate hydrogen abstractions by the nitro group. Ward<sup>4</sup> observed an esr signal upon irradiation of nitrobenzene and attributed it to radical 1 formed by abstraction of a hydrogen (or deuterium) from tetrahydrofuran, tetrahydrofuran-3,3,4,4- $d_4$  and tetrahydrofuran- $d_8$ .



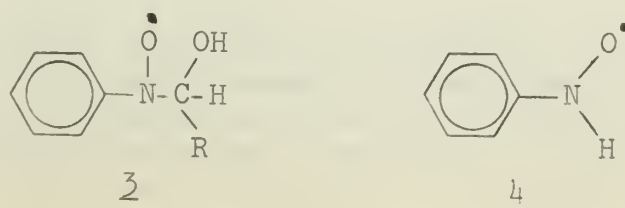
Cowley and Sutcliffe<sup>5</sup> recently reported identical findings and suggested that the observed radical possessed structure 2; this reassignment was based on the belief that the observed proton ( $R_1$ ) hyperfine splitting, 0.4 gauss, was too small for the proton to be attached

directly to the oxygen. They presented scheme 1, which includes an hydrogen abstraction, as a possible route to the formation of 2.

Scheme 1



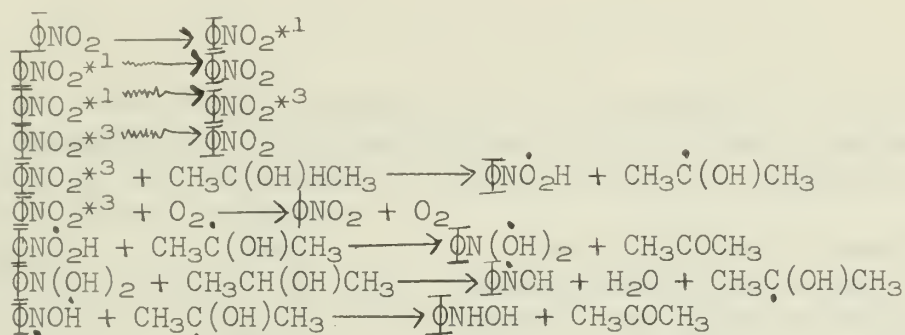
Chachaty and Forchioni<sup>6</sup> reported observing esr signals after irradiation of nitrobenzene in alcoholic solvents. They proposed that radicals 3 and 4 were formed in primary and secondary alcohols respectively. Irradiation of nitrobenzene in *t*-butyl alcohol gave no signal for radical formation while irradiation of it in ethanol revealed a transitory radical with hyperfine splitting similar to that observed by Ward. It was attributed to radical 1.





The irradiation of nitrobenzene in isopropyl alcohol was reported by Hurley and Testa<sup>7,8</sup> to initially give phenylhydroxylamine, which subsequently formed nitrosobenzene and azoxybenzene in dark reactions. Nitrobenzene was found to be photochemically inert in benzene solution<sup>7</sup>. A 30% increase in quantum yield ( $0.87 \times 10^{-2}$  to  $1.44 \times 10^{-2}$ ) was found upon exclusion of oxygen from the alcoholic solvent, indicated less quenching of the triplet state. Isolation of acetone, generated in the photolysis at a rate double that of the nitrobenzene decomposition, provided direct evidence for hydrogen abstraction from the isopropyl alcohol. The mechanism indicated in scheme 2

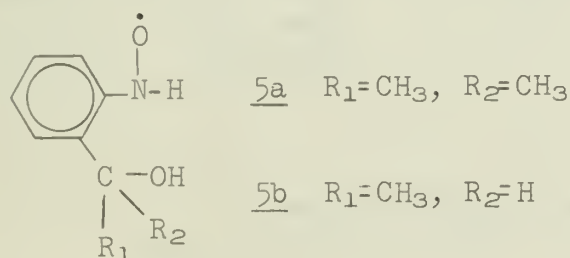
Scheme 2



was suggested as an explanation for the above results. The vapor phase photolysis of nitrobenzene was investigated earlier by Hastings and Matsen<sup>9</sup> and found to yield nitrosobenzene and *p*-nitrophenol. Further evidence for photoreductions was presented through the photolysis 4-nitrobenzoate esters in the formation of 4-aminobenzoate esters<sup>10</sup>. Transesterifications with the ethanol solvent were observed with this reduction but there was no attempt made to find solvent oxidation products.

Further conclusive evidence for hydrogen abstraction by the  $n, \pi^*$  excited state of nitro aromatics were presented by Morrison and Migdalof<sup>11</sup> through studies of the irradiation of *o*-nitrotoluene in a mixture of dioxane and D<sub>2</sub>O. Infrared and nmr analysis indicated an average of 1.6 deuteriums per molecule were incorporated into the methyl group with the following distribution (mass spectrometry): 10% d<sub>0</sub>, 33% d<sub>1</sub>, 40% d<sub>2</sub> and 17% d<sub>3</sub>. It was also shown that no deuterium incorporation occurred in the dark, and that *p*-nitrotoluene did not abstract deuterium under identical conditions.

Evidence was also presented that *o*-nitroalkylbenzenes gave other reactions along with hydrogen abstraction. Strom and Weinstein<sup>12</sup> observed esr signals upon irradiation of *o*-nitrotoluene, *o*-nitroethylbenzene and *o*-nitrocumene. There was no attempted analysis of the radical formed from *o*-nitrotoluene because of the poor quality of the spectra obtainable. Comparison of the experimental and theoretically calculated spectra for the radicals formed from *o*-nitroethylbenzene and *o*-nitrocumene allowed for complete analysis of the esr spectra. It was suggested that the radical (5) was formed by intramolecular hydrogen abstraction and rearrangement followed by hydrogen donation from a different molecule. No esr signal was observed following the irradiation of the *para* isomer under identical conditions.



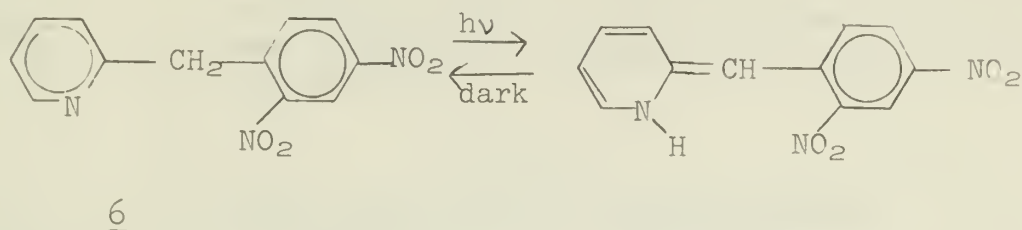
## PHOTOCHROMISM

A direct consequence of hydrogen abstraction of excited nitro groups is the photochromic behavior of certain aromatic nitro compounds. A photochromic system has the ability to undergo a photochemically induced reversible change, and in the absence of light reverts back to the original state<sup>13,14</sup>. Photochromism of aromatic nitro compounds was observed by Tschitschibabin<sup>15</sup>, who observed a color change upon

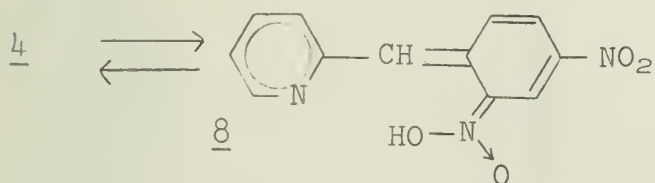




irradiation of solid 2-(2,4-dinitrobenzyl)-pyridine (6). He proposed a mechanism involving hydrogen transfer from the benzyl carbon to the ring nitrogen based on the finding that no photochromic behavior was observed for 4-(2,4-dinitrobenzyl)-pyridine (7).

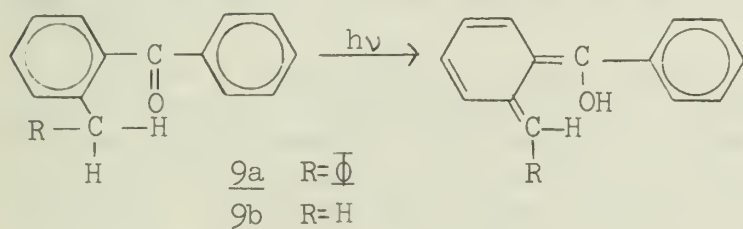


Hardwick and co-workers<sup>16</sup> suggested the involvement of the nitro group in forming the aci-nitro compound (8). The observation of photochromic behavior in both isopropyl alcohol solution and in a glass led these workers to suggest that this process was not dependent on crystal structure.



The basis for the mechanism proposed by Tschitschibabin was shown to be invalid<sup>17</sup>. Although 7 was found to be inactive in the solid state, 7 was found to be capable of undergoing a photochromic change at low temperatures in solution. Irradiation of 7 in an equal-volume mixture of ethanol and *t*-butyl alcohol gave a faint purple color at room temperature, and an intense purple color was observed in ethanol glass at  $-180^{\circ}$ . These colors faded rapidly upon warming to room temperature in the dark. The aci-nitro structure would account for these results and at the same time account for the unimolecularity of the process through a six-membered ring transition state for hydrogen abstraction.

A more definitive investigation into the exact structural requirements of photochromic aromatic nitro compounds was conducted by Margerum and co-workers<sup>18</sup>. The pyridine ring was shown not to be essential to photochromism as indicated by the findings that 2,4,2',4'-tetranitrodiphenylmethane, 2,4,4'-trinitrodiphenylmethane, and the N-oxides of 6 and 7 were strongly photochromic. Another requirement was shown to be the existence of activated benzylic hydrogens ortho to the nitro group. The 2-nitro-4-cyanophenyl and the original 2,4-dinitrophenyl groups were shown to be effective activators<sup>19,20</sup>. It was demonstrated that the replacement of the  $\text{CH}_2$  by a CO group resulted in the loss of activity. The photochromism of ortho-benzylic nitro compounds is analogous to the photochemically induced enolization of *o*-benzylbenzophenone (9a) and *o*-methylbenzophenone (9b) reported by Yang and Rivas<sup>21</sup>.



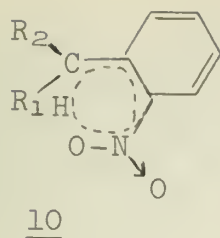
A kinetic study<sup>20,22</sup> of the fading reactions of various photochromic aromatic nitro compounds indicated that an activated complex was formed. The large decrease in the entropy of activation of various compounds (Table 1) in ethanol, indicated that the activated complex (10) was more rigid than the ground state.

Table 1

Values of  $E_a$ ,  $\Delta S$  and  $k$  for the Fading Reaction

Compound	$E_a$ (kcal. mole <sup>-1</sup> )	$\Delta S^*(\text{eu})$	$k \times 10^3 (\text{sec}^{-1})$
2-(2,4-dinitrobenzyl)-pyridine ( <u>6</u> )	5.8±0.1	-44	
2-(2-nitro-4-cyanobenzyl)-pyridine	4.7±0.1	-46	
Methyl bis(2,4-dinitrophenyl) acetate	5.6±0.1	-45	6.03
Ethyl bis(2,4-dinitrophenyl) acetate	5.4±0.1	-50	0.755
2,4,4'-trinitrodiphenylmethane	5.4±0.1	-50	0.695
2,4,2',4'-tetranitrodiphenylmethane	5.5±0.1	-47	2.84



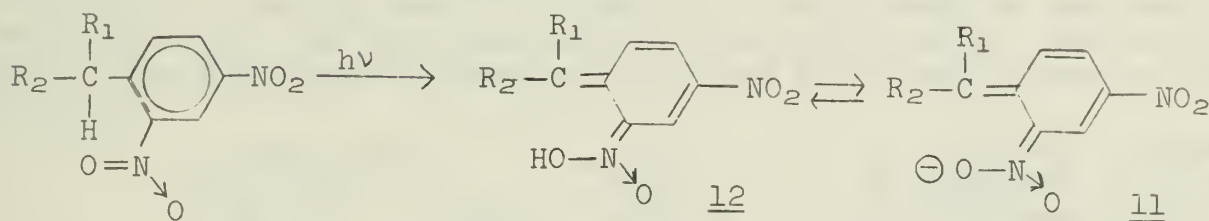


Weinstein, Blum and Sousa<sup>23</sup> have investigated the photochromism of various 2-(2-nitro-4-substituted benzyl)-pyridines in ethanol by flash photolysis. The first-order rate constants of the fading reaction increased with increasing electron donating properties of the substituent, and the log  $k$  values were found to be linearly proportional to the Hammett  $\sigma_p$  values (See Table 2).

Table 2

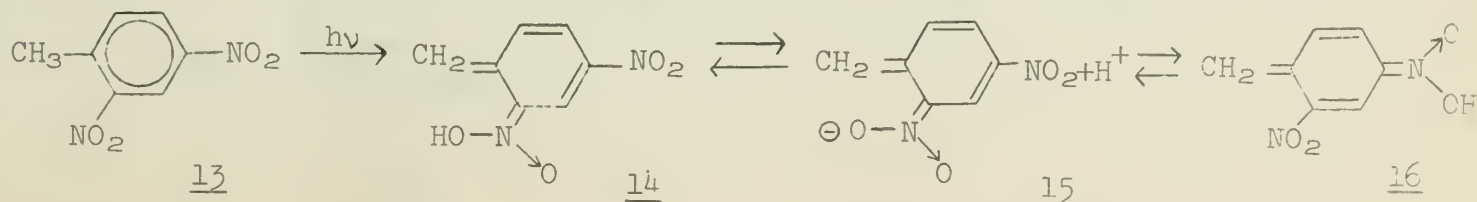
## Substituent effects of photochromism

4-substituent	$k(\text{sec}^{-1})$	$t_2^1(\text{msec})$	$\sigma_p$
NH <sub>2</sub>	$370 \times 10^1$	0.187	-0.660
OH	329	2.11	-0.357
H	56.3	12.3	0.0
Cl	27.4	25.3	0.227
CO <sub>2</sub>	26.3	26.3	0.132
CONH <sub>2</sub>	5.94	117	-
CO <sub>2</sub> Et	2.45	283	0.522
CO <sub>2</sub> Me	2.42	286	0.463
C≡N	1.17	592	0.628
NO <sub>2</sub>	0.122	$568 \times 10^1$	0.778



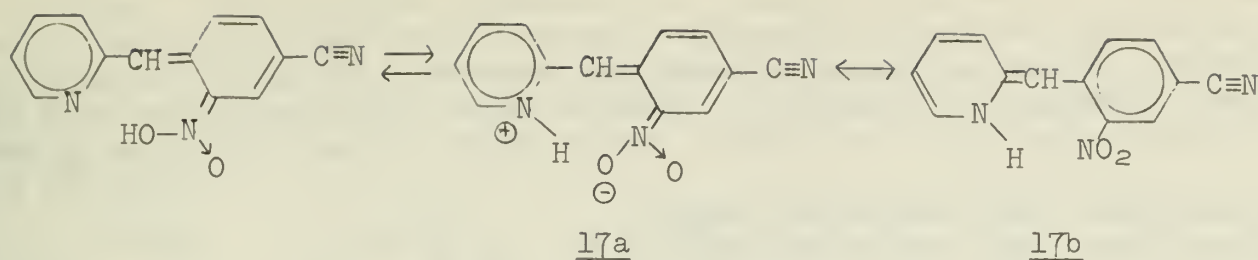
To obtain more information about the structure of the aci-nitro compounds, Margerum and co-workers<sup>18</sup> compared the uv spectra of the parent compounds in the presence of base with those of the respective aci-nitro compounds. Owing to the similarity of the spectra these workers depicted the mechanism as a hydrogen abstraction by the nitro group to form aci-nitro compound (12) in equilibrium with its conjugate base 11. The spectra of the photochromic pyridine compounds were different from the anionic species because the basicity of the ring nitrogen allowed some contribution from a protonated pyridine form similar to the structure originally postulated by Tschitschibabin.

Using a less complex system, Wettermark and Ricci<sup>24</sup> observed that the flash photolysis of 2,4-dinitrotoluene (13) resulted in formation of an aci-nitro species having a pH-dependent fade reaction. These photolyses were carried out in aqueous solution (1% ethanol by volume) at 30° with some formation of some permanent photo-products. The ortho-aci-nitro species (14) was suggested as the photochemically generated material in equilibrium with its conjugate base (15) and the para-aci-nitro species (16). These workers also estimated the pK<sub>a</sub> of the aci-nitro species to be about 1. By comparison o-nitrotoluene was determined<sup>25</sup> to have pK<sub>a</sub>=4. Based on these findings, Wettermark and Sousa<sup>19</sup> suggested that the photoinduced abstraction of the hydrogen in compounds like 2-(2-nitro-4-cyanobenzyl)-pyridine involved the formation of the corresponding aci-nitro compound which, in turn, was almost totally converted to the N-protonated species 17.





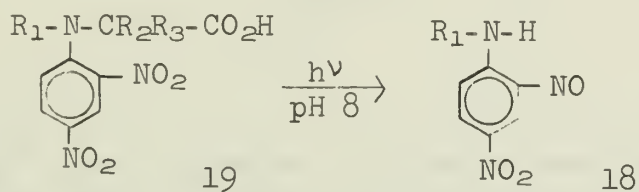




## PHOTOCHEMISTRY OF CONJUGATED AROMATIC NITRO COMPOUNDS

Some of the early aspects of the photochemistry of aromatic nitro compounds have been covered in general reviews on photochemistry<sup>26, 27</sup>. An initial hydrogen abstraction by the nitro group was suggested for some of these reactions. The photochemically induced aromatic substitutions of nitro aromatics have been recently discussed<sup>28</sup> with an emphasis on the theoretical aspects of the directing abilities of substituents on the ring.

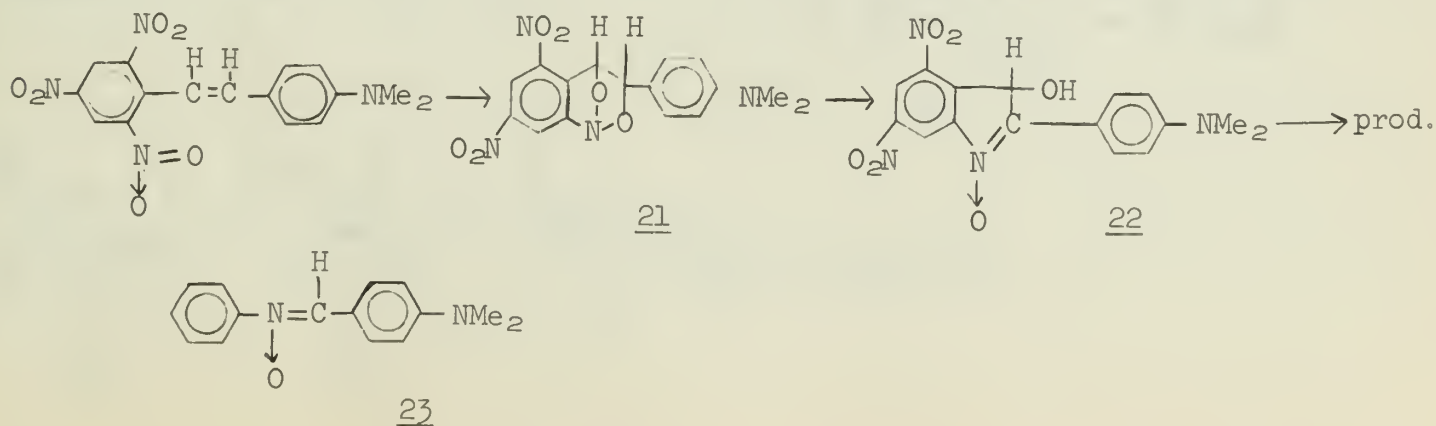
Russell<sup>29</sup> has observed the formation of N-substituted-4-nitro-2-nitrosoanilines (18) upon irradiation of the appropriate N-(2,4-dinitrophenyl) amino acids (19) at pH 8. It was suggested that this reaction did not involve a hydrogen abstraction by the excited state since this reaction proceeded at similar rates when R<sub>1</sub> was either a hydrogen or a methyl group. It was also noted that when R<sub>2</sub> and R<sub>3</sub> were methyl and phenyl groups, the reaction was still observed, thus eliminating the possibility of hydrogen abstraction from the carbon atom α to the amino group. However, there was no report of the photochemical reaction of 19 when R<sub>1</sub>, R<sub>2</sub> and R<sub>3</sub> were all different from hydrogen.



Pollitt<sup>30</sup> observed that the formation of 18 from 19 at pH 2 occurred to give 70% of the yield obtained at pH 8. The mechanistic pathway is still not fully understood. Meadle and Pollitt<sup>31</sup> studied the photo-

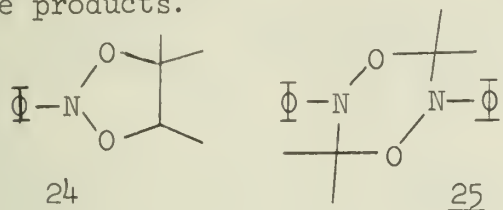
chemical formation of 2-substituted-6-nitrobenzamidazole-1-oxide (20) from N-(2,4-dinitrophenyl) amino acid (19 R<sub>1</sub>-R<sub>2</sub>=H); the maximum yield occurring at pH 3. The reaction appeared to be a general process for compounds of this type possessing α hydrogens. The pH dependence of product formation was a prominent feature of these reactions. No speculation concerning the possible mechanism responsible for these results was offered.

Splitter and Calvin<sup>32</sup> indicated that the photochemical transformation of 2,4,6-trinitro-4'-dimethylaminostilbene to form 21 may involve addition of the nitro group to the double bond in a two-step process. Intermediate 21 presumably decomposed to an intermediate nitrone (22) which in turn formed products. The evidence for 22 was based on formation of an intermediate having a uv absorption spectrum resembling the chromophore of 23. There appears to be no concrete evidence for the formation of 21.

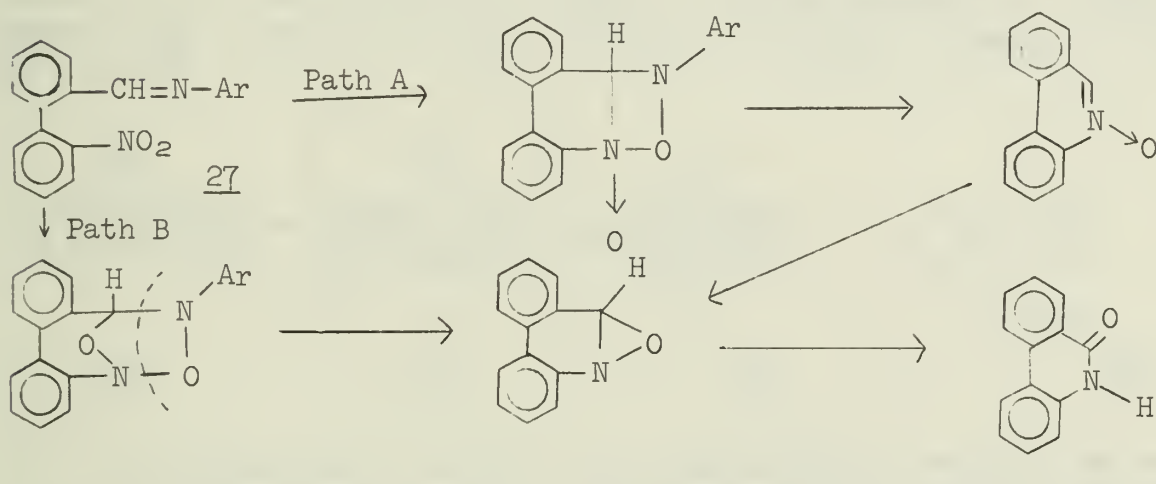




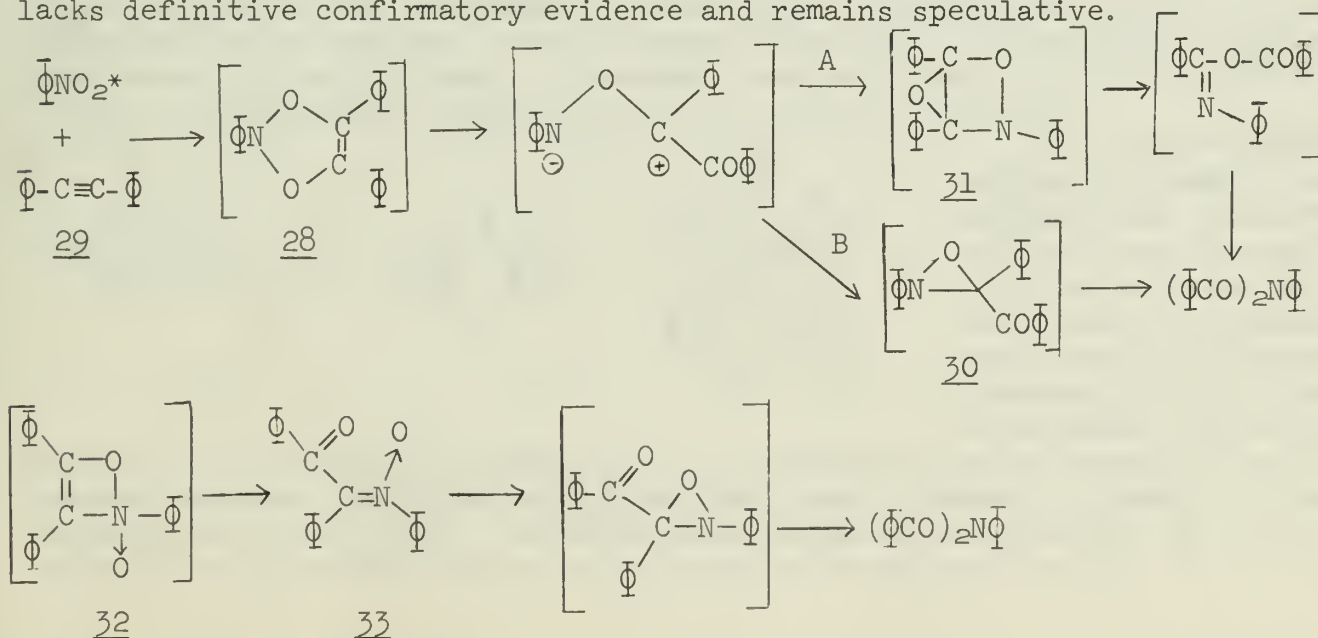
In an attempt to find a cycloaddition of a nitro group to an olefin which would be analogous to the oxetane formation from ketones and aldehydes, Büchi and Ayer<sup>33</sup> photolyzed nitrobenzene in the presence of 2-methyl-2-butene. Instead of the desired 1,3,2-dioxazolidine (24), acetone, acetaldehyde, N-phenylacetamide, azobenzene and a neutral material (25) were isolated. A speculative mechanistic sequence involving 24 as an intermediate based in part on Splitter's work was proposed to explain the products.



Taylor, Furth and Pfau<sup>34</sup> reported the formation of 5(6H)phenoanthridone (26) upon irradiation of the p-chlorophenyl anil of o-nitro-o'-formylbiphenyl (27). Of the two pathways proposed, path B was favored over path A because of the precedent set by Büchi and Splitter using the 1,3,2-dioxazolidine intermediate.



Scheinbaum<sup>35</sup> also suggested a photocycloaddition involving the unstable 1,3,2-dioxazole (28) to explain some of the products formed in the photoinduced reaction of nitrobenzene with toluene (29). The path thought to be more likely, path B, involved the formation of an oxazirane intermediate (30); path A involved the more strained intermediate (31). An alternate mechanism considered involved the formation of 32 which then would proceed through nitrone 33 to form products. Thus, the basic postulate of a cycloaddition of a photoexcited nitro group with an unsaturated system still lacks definitive confirmatory evidence and remains speculative.

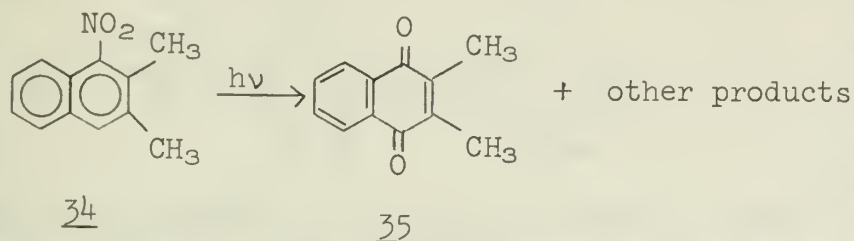




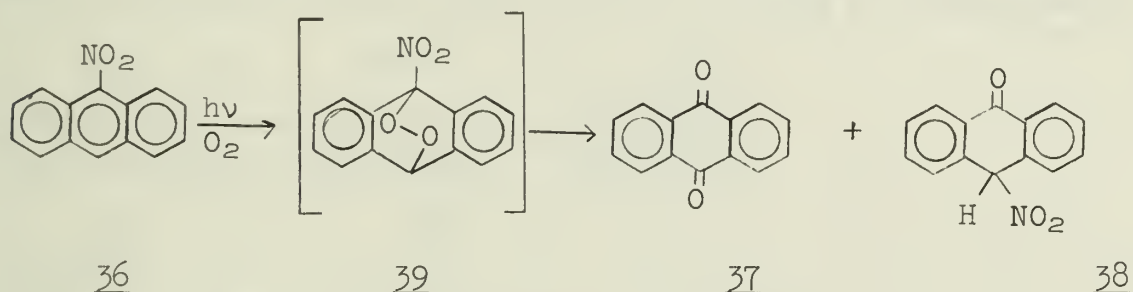


PHOTOCHEMISTRY OF NONCONJUGATED AROMATIC NITRO COMPOUNDS

Photolysis of 2,3-dimethyl-1-nitronaphthalene (34) was found by Chapman and co-workers<sup>36</sup> to form 2,3-dimethyl-1,4-naphthaquinone (35) and several other products thought to be formed by attack on the methyl groups.

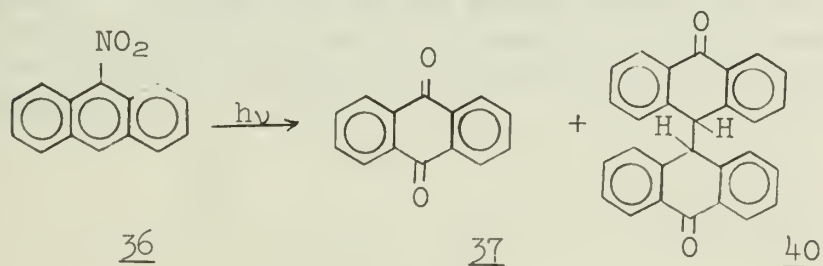


An analogous reaction, reported earlier by Dufraisse and Priou<sup>37</sup>, involved the irradiation of 9-nitroanthracene (36) to produce anthraquinone (37) and 10-nitroanthrone (38). The reaction was thought to proceed through an intermediate 9,10-epidioxide (39) formed by direction addition of oxygen. Attempts to isolate peroxide (39) failed.



It was suggested by Greene<sup>38</sup> that the anaerobic reaction was wavelength dependent since 420-530 mμ light gave bis-9-nitroanthracene and 370-410 mμ light gave 10,10'-bianthrone (40) and nitrogen (II) oxide. This wavelength dependence may be compared with the analogous results found by Yang and co-workers<sup>39,40</sup> in the 9-anthraldehyde and 9-acetylanthracene systems. These workers suggested that the  $\pi, \pi^*$  triplet may be low-lying with its excitation energy primarily localized in the aromatic ring system therefore favoring dimerization whereas the energy of the  $n, \pi^*$  triplet could be primarily localized in the substituent group. This interpretation assumed that the  $n, \pi^*$  triplet was not affected by conjugation.

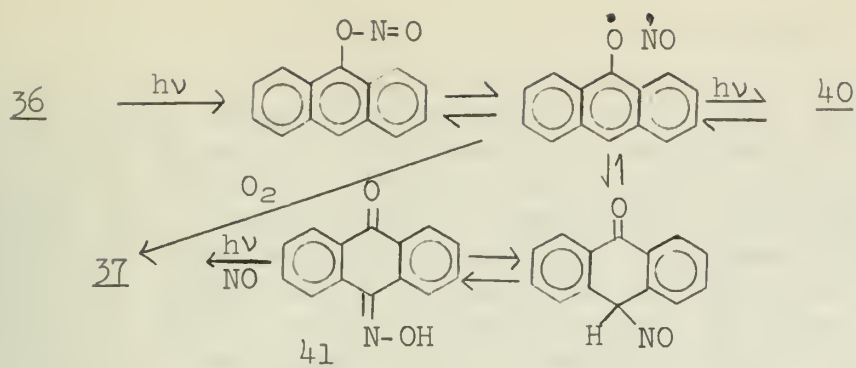
When Chapman and co-workers<sup>41</sup> irradiated 9-nitroanthracene (36) in the absence of oxygen with a mercury arc lamp and pyrex filter, both anthraquinone (37) and 10,10'-bianthrone (40) were formed. It seemed reasonable that the  $n, \pi^*$  triplet excited state of (36) was initially responsible for the observed reaction.



The following facts made the suggested scheme a reasonable rationale for this reaction. The anthraquinone nonoxime (41) could be isolated in up to 20% yield under controlled conditions and it could be subsequently converted to 37 in the presence of nitrogen (II) oxide. The

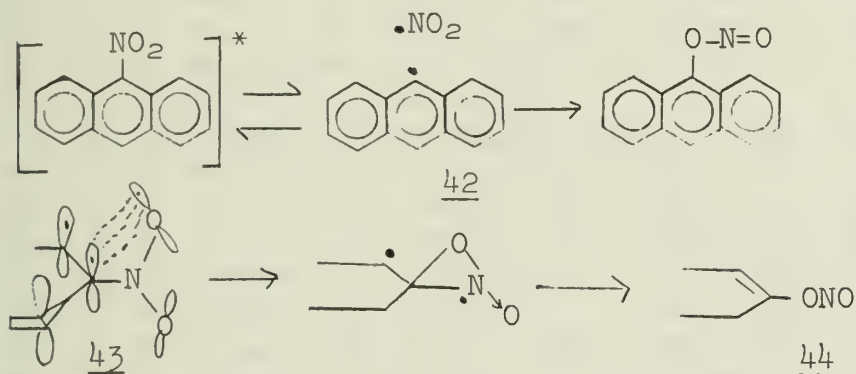
addition of nitrogen (II) oxide to the irradiated solution increased the yield of 37, whereas sweeping the solution with an inert gas to remove nitrogen (II) oxide increased the yield of 40. The addition of oxygen to the solution gave an increase in the yield of 37 which could also be formed by irradiation of 40.





The conversion of the nitro group to a nitrite group is not a general conversion since nitrobenzene is stable under the above reaction conditions. This rearrangement may have analogies in the formation of oximes from olefinic nitro compounds<sup>42</sup>. The difference in these reactions was thought to correlate with the fact that the nitro group was out of the

plane of the aromatic or olefinic systems. Of the two mechanisms presented for nitrite formation, dissociation-recombination or an intramolecular rearrangement, the former has been eliminated. If dissociation did occur the nitrogen (IV) oxide and 9-anthryl radicals (42) formed would diffuse apart and both nitrogen (IV) oxide and anthracene should be isolatable. Neither was found. The intramolecular rearrangement can be more conveniently rationalized in terms of the  $n, \pi^*$  excited state, arguing that the nitro group is out of the plane of the aromatic ring. With this geometry (43) the half-vacant non-bonding orbitals on oxygen might overlap with the orbitals of the ring and the nitrite (44) structure formed by rearrangement.



## CONCLUSION

Much of the photochemistry of aromatic nitro compounds has been found to originate from the  $n, \pi^*$  excited state. Hydrogen abstraction appears to be a common and well characterized mode of reaction both in photoreductions of the nitro group and the photochromic behavior of many aromatic nitro compounds. However the photocycloadditions of the nitro group suggested in certain reaction sequences are not based on definitive evidence and are highly speculative. The geometrical arrangement of the nitro group relative to the aromatic system apparently influences the reactivity of the  $n, \pi^*$  excited state. Many of the photochemical reactions of aromatic nitro compounds require further investigation before definitive mechanistic conclusions may be drawn. Although there are several analogies between the photochemistry of aromatic aldehydes and ketones and of aromatic nitro compounds, much work remains to be done before the similarities and dissimilarities in their photochemistry can be fully understood.





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# RECENT APPLICATIONS OF CARBON-13 NMR SPECTROSCOPY

Reported by Steven Beare

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## INTRODUCTION

The utility of  $^{13}\text{C}$  magnetic resonance spectroscopy has dramatically increased in the past few years, due in most part to technological advances.  $^{13}\text{C}$  nmr studies prior to 1965 have been thoroughly discussed in a seminar<sup>1</sup> and several reviews,<sup>2-4</sup> while recent seminars have described 1) the technological advances in nmr spectroscopy as applied to the  $^{13}\text{C}$  nucleus<sup>5</sup> and 2) theoretical aspects of carbon-proton spin-spin coupling constants,<sup>6</sup> with a few illustrative applications.

The intent of this seminar is to show the potential of  $^{13}\text{C}$  nmr spectroscopy in supplying useful information in current applications involving bond hybridization, conformational analysis, elucidation of proton nmr assignments, and the determination of the electronic structure of molecules.

## EXPERIMENTAL TECHNIQUES

One of the prime factors responsible for the time lag in practicality of  $^{13}\text{C}$  nmr compared to proton and fluorine nmr lies in the low natural abundance (1.1%) of the carbon-13 isotope. This is perhaps fortuitous, for if the most abundant isotope of carbon possessed a nuclear spin of  $\frac{1}{2}$ , as does  $^{13}\text{C}$ , most organic compounds would give rise to inordinately complicated nmr spectra.

In addition to its low natural abundance,  $^{13}\text{C}$  has a low sensitivity to nmr detection (1.6% relative to hydrogen at constant field) and relatively long relaxation times (minutes for most organic compounds), making it especially susceptible to saturation effects.

At the most commonly used magnetic field strength of 14.092 kilogauss, the  $^{13}\text{C}$  nucleus has a resonance frequency of 15.085 MHz, while the  $^{13}\text{C}$  chemical shifts of most organic compounds fall over a range of 400 ppm, approximately the range of  $^{19}\text{F}$  chemical shifts.<sup>2</sup>

Most of the initial  $^{13}\text{C}$  nmr work was pioneered by Lauterbur,<sup>7</sup> who partially overcame  $^{13}\text{C}$  sensitivity problems by using large diameter nmr tubes, operating in the dispersion mode with high RF levels, and using rapid sweep rates to avoid saturation. Later workers<sup>2</sup> found that a considerable improvement in resolution was possible by operating in the absorption mode (as is done in  $^1\text{H}$  and  $^{19}\text{F}$  nmr), whereby slower sweep rates could be used. Recent developments<sup>5</sup> which have made possible high quality  $^{13}\text{C}$  nmr spectra are internuclear double resonance (INDOR),<sup>8</sup> proton decoupling,<sup>9</sup> and the use of computer time-averaging (CAT),<sup>10</sup> made possible by improved field-frequency stabilization techniques.

## $^{13}\text{C}$ -H SPIN-SPIN COUPLING

Because carbon-13 possesses a nuclear spin of  $\frac{1}{2}$ , it exhibits spin-spin coupling with neighboring atoms possessing a spin of  $\frac{1}{2}$ , such as hydrogen and fluorine. Furthermore, since the magnitudes of directly bonded carbon-proton coupling constants are relatively large ( $\sim 120$  to  $280$  Hz), and the shielding constants for  $^{13}\text{C}$  nuclei are quite sensitive to small changes in electronic environment, the relatively poor resolution and signal-to-noise ratios accessible to earlier workers were not a deterrent to the gathering of much data.

One of the most useful observations regarding  $^{13}\text{C}$ -H coupling constants has been the relatively good correlation between  $J_{\text{C-H}}$  and C-H bond hybridization,<sup>11</sup> the theoretical and empirical bases for which have been extensively discussed.<sup>6</sup> The empirical relationship is  $\%s \text{ character} = 0.2 J_{\text{CH}}$  (eq 1).

Because of the relatively poor resolution available to earlier workers in the  $^{13}\text{C}$  nmr region, as well as the relative accessibility of  $^1\text{H}$  nmr,  $^{13}\text{C}$ -H coupling constants have quite frequently been measured from the proton spectrum. At high amplitudes the spectrum resulting from the 1.1%  $^{13}\text{C}$  adjacent to hydrogen may be observed, referred to as the  $^{13}\text{C}$  satellite spectrum.







APPLICATIONS TO MOLECULAR STRUCTURE-- $J_{13C-H}$ 

One of the initial applications of the relationship between  $J_{CH}$  and bond hybridization was effected by Olah and coworkers<sup>12</sup> in defense of the postulated stable carbonium ion resulting from the ionization of isopropyl chloride in antimony pentafluoride-sulfur dioxide solution.<sup>13</sup> The initial publication reported a value of  $J_{CH} = 382$  Hz for  $(CH_3)_2^{13C-H^+}$ , interpreted as evidence for an  $sp^3$ -hybridized donor-acceptor complex, although application of equation 1 predicts over 75% s character for the C-H bond.<sup>11</sup> A reinvestigation by Olah and Comisarow,<sup>14</sup> using  $^{13}C$  enriched isopropyl chloride and an "improved system," showed the first work to be in error; a new value for  $J_{CH} = 168$  Hz, indicating 33.6% s character,<sup>11</sup> was obtained. The absorptions previously assigned to  $^{13}C$  satellite peaks were considered to be due to impurities. The excellent agreement between the calculated and assumed  $sp^2$ -hybridization of the central carbon atom in carbonium ions was interpreted as proof of the generality of the linearity between  $J_{C-H}$  and fractional s character. However, it is more reasonable that such good agreement was for the most part fortuitous, since other workers have found electronegative substituents to dramatically influence the value of  $J_{C-H}$  in substituted methanes.<sup>11,15</sup>


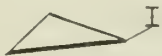


## CYCLOPROPANE

A considerable amount of energy has been expended in defining the hybridization in cyclopropanes; it appears, from a variety of physical methods,<sup>16</sup> to be close to  $sp^2$  for the C-H bonds.

Muller and Pritchard<sup>11</sup> assigned the carbon orbitals used to form the carbon-proton bonds in cyclopropane 32% character from the C-H coupling constant of 161 Hz. This assignment appears to be justified on the basis of the good correlation between  $J_{C-H}$  and % s character in hydrocarbons.<sup>11</sup>

Footo<sup>17</sup> has suggested that since the C-H bonds in cycloalkanes have more s character than the corresponding open-chain analogs, the carbon-carbon bond should have more p character, namely  $sp^5$ .<sup>16</sup> Weigert and Roberts<sup>18</sup> have recently utilized  $^{13}C$ - $^{13}C$  coupling constants to elegantly show the  $sp^5$  character in the carbon-carbon bond of substituted cyclopropanes. Frei and Bernstein<sup>19</sup> had earlier studied carbon-carbon couplings in several  $^{13}C$  enriched compounds, finding that  $J_{C-C}$  is simply proportional to the product of the s characters of the two hybrid orbitals used in forming the bond. Pople and Santry<sup>20</sup> later justified this approach by MO calculations, developing a semiempirical relationship which Weigert and Roberts used to calculate a value for  $J_{C-C}$  in cyclopropane of 15 Hz, assuming  $sp^5$  hybridized carbon-carbon bonds.<sup>18</sup> By using time-averaging techniques (several hundred scans), they were able to measure the natural abundance (0.02%)  $^{13}C$ - $^{13}C$  coupling constants for several cyclopropane derivatives (Table 1). The observed coupling constants are in good agreement with the concept of  $sp^5$  hybridization of the orbitals used in forming the internal bonds and  $sp^2$  hybridization of the orbitals used in forming the external bonds, as pictured in current models of cyclopropane.<sup>16</sup> As a point of comparison for the ring carbon to methyl bond in methylcyclopropane,  $J_{C-C} = 44.2$  Hz for the methyl to ring bond in toluene,<sup>19</sup> formed from an  $sp^3$ - and  $sp^2$ -hybridized orbital.

Table 1.  $^{13}C$ - $^{13}C$  Coupling Constants for Cyclopropane Derivatives<sup>18</sup>  $J_{C-C}$  (Hz)

Compound	Bond	Observed	Calculated
 Br	1,2	13.3	15
 I	1,2	12.9	15
 Cl Cl	1,2	15.5	15
 CH <sub>3</sub>	$\alpha, 1$	44.0	46



The self-consistency between the assumed  $sp^5$ -hybridization of the orbitals used in forming the internal bond and the  $sp^2$ -hybridization for the external orbitals would seem to implicate the validity of the  $J_{C-H}$  dependence on hybridization for hydrocarbons. More importantly, this study suggests that  $J_{C-C}$  is a valid reflection of hybridization for electronegatively substituted compounds.

These results are further strengthened by concurrent work of Grant and Litchman,<sup>21</sup> who studied the effect of polar groups on directly bonded carbon-carbon coupling constants in neopentane derivatives (Table 2).

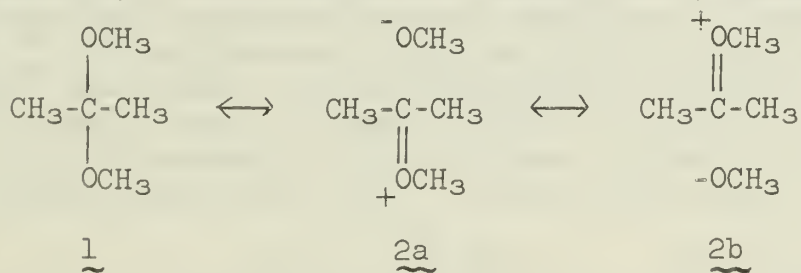
Table 2.  $^{13}C$ - $^{13}C$  Coupling Constants for Neopentane Derivatives

X	$J_{CC}$ in $X(CH_3)_3$ (Hz) <sup>21</sup>	$J_{C-H}$ in $XCH_3$ (Hz) <sup>11</sup>
CH <sub>3</sub>	36.9	126
NH <sub>2</sub>	37.1	133
OH	39.5	141
Cl	40.0	150
Br	40.2	152

The measured values of  $J_{C-C}$  were found to be much less sensitive to directly bonded electronegative groups than  $J_{C-H}$  in analogous methyl derivatives studied earlier by Muller and Pritchard<sup>11</sup> (Table 2). Grant and Litchman suggest that hydrogen experiences inductive effects from substituents more than carbon because no transfer of inductive charge to neighboring groups is possible. It might have been informative to have measured the carbon-hydrogen coupling constants in the neopentane derivatives in order to see if the methyls experienced any of the effects of charge delocalization as suggested by Grant and Litchman.

#### DOUBLE BOND-NO BOND RESONANCE

Pletcher and Cordes<sup>22</sup> have utilized  $^{13}C$ -H coupling constants in order to determine the extent of double bond-no bond resonance, if any, in ketals, ortho esters and orthocarbonates, suggested by Hine<sup>23</sup> to account for their unexpected order of reactivities to hydrolysis relative to expected carbonium ion stabilities. Since the magnitude of  $J_{C-H}$  is related to the electronegativity of the substituent on the carbon of interest,<sup>11</sup> Pletcher and Cordes hoped to see increasing carbonium ion character for the oxygen-bonded carbon reflected in  $J_{C-H}$  for the series, ethers  $\rightarrow$  ketals  $\rightarrow$  ortho esters. Ethers have no additional structures due to double bond-no bond resonance, while ketals (1) have two (2a and 2b) and ortho esters have six. However, their results were inconclusive, as shown in Table 3,



partly due to the absence of obvious trends in both  $J_{CH_3}$  and  $J_{OCH_3}$ , and also from the lack of a suitable model with which to gauge  $J_{C-H}$ .

Table 3.  $^{13}C$ -H Coupling Constants in Ethers, Ketals, and Ortho Esters<sup>22</sup>

Compound	$J_{CH_3}$ (Hz)	$J_{OCH_3}$ (Hz)
Methyl acetate	130	147
Methyl t-butyl ether	125	140
2,2-Dimethoxypropane	127	142
Methyl orthoacetate	126	144

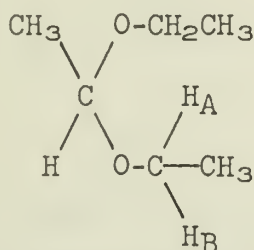




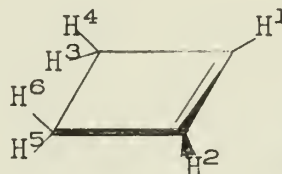
## ELUCIDATION OF PROTON NMR ASSIGNMENTS

A particularly useful application of carbon-proton coupling constants is in the elucidation of proton nmr spectra, where proton-proton coupling parameters may occasionally lead to ambiguous assignments.<sup>24,25</sup> For example, Rattet, Mandell, and Goldstein<sup>24</sup> have recently resolved the proton nmr spectrum of acetaldehyde diethyl acetal (3), in which the methylene protons form an AB system.

Previously, two strikingly different sets of coupling constants had been obtained which were both consistent with the experimentally observed spectrum. Goldstein and coworkers measured the  $^{13}\text{C}$ -H coupling constants as well as the proton-proton coupling constants, and by requiring that both sets of coupling parameters be simultaneously consistent, a unique set of J values was obtained.



3



4

A recent interpretation of the nmr spectrum of cyclobutene by Hill and Roberts<sup>25</sup> has emphasized the importance of including long-range carbon-proton couplings as well as those arising from directly bonded atoms.

Cyclobutene (4) gives a simple two line proton nmr spectrum, although Borčić and Roberts showed that the magnetic equivalence of the two vinyl protons and the two sets of methylene protons in 4 could be removed by an examination of the  $^{13}\text{C}$  satellite spectrum.<sup>26</sup> By matching calculated and observed spectra for cyclobutene and cyclobutene-1,2-d<sub>2</sub>, they derived a complete set of proton-proton coupling constants.

However, a more recent nmr examination by Weigert and Roberts<sup>25</sup> of additional deuterated cyclobutenes, -3,3-d<sub>2</sub>, -2,3,3-d<sub>3</sub> and -1,3,3-d<sub>3</sub>, has resulted in proton-proton coupling constants in disagreement with the earlier study. Experimental and calculated  $^{13}\text{C}$  satellite spectra could only be matched by the inclusion of three- and four-bond carbon-proton coupling constants in the calculations, as well as artificially introduced chemical shifts between the vinyl protons H<sub>1</sub> and H<sub>2</sub> and the methylene protons H<sub>3</sub> and H<sub>5</sub> in 4.

Other compounds whose  $^{13}\text{C}$  spectra have recently been studied to gain a better understanding of their proton nmr spectra are: pyridines,<sup>27</sup> benzene,<sup>28,29</sup> fused aromatic compounds,<sup>30</sup> p-benzoquinones,<sup>31</sup> 4-pyrone,<sup>32</sup> acroleins<sup>33</sup> and cyclopropanes.<sup>34</sup>

One such study<sup>28</sup> has yielded a potentially useful correlation between  $J_{\text{CH}}$  and  $J_{\text{HH}}$ . In 1962 Karabatsos, Graham, and Vane derived a relatively simple relationship between  $J_{\text{CH}}$  and  $J_{\text{HH}}$  on the assumption that the Fermi contact term is the sole contributor to the coupling (equations 2-4).<sup>35</sup> However, when these workers applied the

Equation 2	$J_{\text{C-H}} = 0.3 J_{\text{H-H}}$	(for $\text{sp}^3$ -hybridized $^{13}\text{C}$ )
Equation 3	$J_{\text{C-H}} = 0.4 J_{\text{H-H}}$	(for $\text{sp}^2$ -hybridized $^{13}\text{C}$ )
Equation 4	$J_{\text{C-H}} = 0.6 J_{\text{H-H}}$	(for $\text{sp}$ -hybridized $^{13}\text{C}$ )

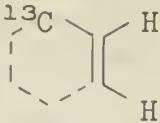
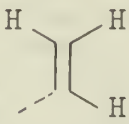
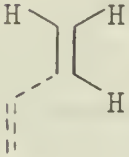
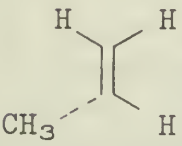
equations to a series of aliphatic compounds, quite poor agreement was observed between the calculated and experimental constants.

Recently Weigert and Roberts measured all four of the carbon-proton coupling constants in benzene.<sup>28</sup> They applied equation 3, in the forms  $J_{\text{C-C-H}} = 0.4 J_{\text{H-C-H}}$  and  $J_{\text{C-C-C-H}} = 0.4 J_{\text{H-C-C-H}}$ , to known long-range proton-proton couplings in model compounds containing the vinyl moiety and obtained excellent agreement with the observed carbon-proton couplings in benzene (Table 4).

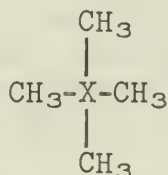
More recently Weigert, Winokur, and Roberts<sup>36</sup> have measured  $J_{\text{C-X}}$ ,  $J_{\text{C-X-C-H}}$ , and  $J_{\text{C-H}}$  in tetramethyl derivatives of group IV elements ( $\sum \text{X} = \text{C}, \text{Si}, \text{Ge}, \text{Sn}, \text{and Pb}$ )



Table 4. Relationship of  $^{13}\text{C}$ -H and H-H Coupling Constants<sup>28</sup>

		$J_{\text{C-C-H}}$	$J_{\text{C-C-C-H}}$
Benzene		+ 1.0 (observed)	+ 7.4 (observed)
Calculated from $J_{\text{H-H}}$ in Ethylene		+ 1.0	+ 7.6
Butadiene		+ 0.7	+ 6.8
Propene		+ 0.8	+ 6.8

and found good agreement between observed C-X coupling constants and those calculated on the basis of the Fermi contact coupling mechanism of Karabatsos and coworkers<sup>35</sup> (Table 5). However, application of the simplified equation 2 mentioned earlier in this seminar,  $J_{\text{C-C}} = 0.3 J_{\text{C-H}}$ , which relates the  $\text{sp}^3$ -hybridized carbon-carbon coupling in neopentane to the carbon-hydrogen coupling in isobutane yielded J values in poor agreement with those observed for the heavier elements in group IV (Table 5). Since Karabatsos and coworkers developed equations 2 through 4 assuming that the wave functions of the nuclei being compared were similar,<sup>35</sup> it is not unexpected that the carbon-metal coupling constants in 5 do not have a simple relationship with  $J_{\text{C-C}}$  or  $J_{\text{C-H}}$ .



5 X = group IV element

Table 5. Comparison of Observed and Calculated Carbon-Group IV Coupling Constants in Tetramethyl Derivatives of Group IV elements<sup>36</sup>

X	$J_{\text{C-X}}$ Observed (Hz)	$J_{\text{C-X}}$ Calculated (Hz) Fermi-contact Contribution	From $J_{\text{C-X}} = 0.3 J_{\text{C-H}}$
C	36.2	36.2 (assumed)	37.5
Si	51	58.6	61
Ge	--	204	--
Sn	330	369	510
Pb	250	276	720

Other workers<sup>37-41</sup> have recently measured directly bonded carbon-group IV coupling constants, obtaining essentially the same values as Roberts and coworkers.

In view of the reasonable agreement for the predicted relationship between  $J_{\text{C-C}}$  in neopentane and  $J_{\text{C-H}}$  for isobutane (Table 5), other studies are certain to be forthcoming to determine the generality of Karabatsos' equation.

#### CARBON-13 CHEMICAL SHIFTS

It was early recognized that  $^{13}\text{C}$  chemical shifts in substituted methanes have a linear dependence on the electronegativity of the substituent,<sup>7,42</sup> although deviations may be seen for highly polarizable substituents such as the halides. Spiess and Schneider have interpreted the lack of correlation of  $\delta^{13}\text{C}$  with electronegativity for halogen as a result of dispersion effects and neighboring diamagnetic anisotropic effects.<sup>42</sup>





Bucci<sup>43</sup> has quite recently reported that a good empirical correlation exists between  $\delta^{13}\text{C}$  and electronegativity for substituted methanes and ethanes if one takes into account the number of lone electron pairs in the substituent. He suggests that this latter parameter is the major distinction between two substituents of the same electronegativity. The result is an electric field generated by the lone electron pairs, which would agree with the interpretation of Spiesecke and Schneider.<sup>42</sup>

However, Litchman and Grant<sup>44</sup> feel that these explanations do not adequately rationalize the anomalous trends of  $^{13}\text{C}$  chemical shifts in polyhalogenated methanes and have attempted to theoretically justify them using three parameters: charge polarization, steric effects, and electron delocalization. A valence bond approach developed earlier by Cheney and Grant<sup>45</sup> was employed, although the unavailability of exchange integrals for carbon-halogen bonds prevented a calculation of the effect of electron delocalization on  $\delta^{13}\text{C}$ . By successive application of only the first two of the three parameters considered, Litchman and Grant were able to approximate observed chemical shifts for the bromo- and chloromethanes, although lack of structural data for the iodo group precluded calculations on the iodomethanes.<sup>44</sup>

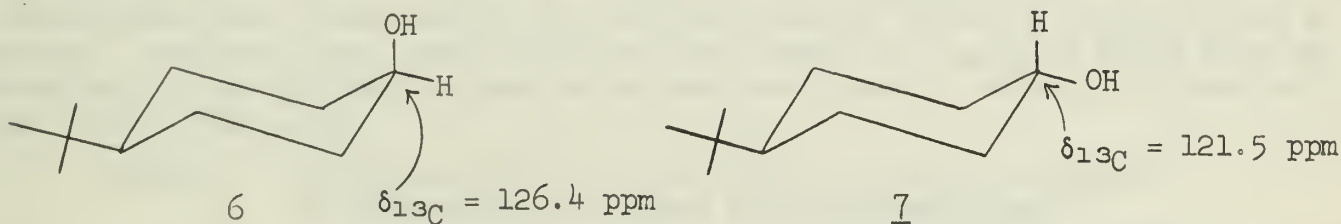
Pugmire and Grant<sup>46</sup> have recently reported a study of the  $^{13}\text{C}$  chemical shifts for a number of six-membered nitrogen heterocycles and their protonated cations. A theoretical analysis using extended HMO wave functions indicated that the chemical shifts are critically dependent on both charge polarization and bond order parameters, and not just  $\pi$ -charge density as was earlier suggested.<sup>47</sup>

A number of studies on the chemical shifts of the carbonyl group in a variety of compounds have shown  $\delta^{13}\text{C}=\text{O}$  to correlate with  $\pi$ -bond polarity,<sup>48</sup>  $n \rightarrow \pi^*$  excitation energies,<sup>49</sup> and the extent of conjugation with neighboring groups.<sup>50,51</sup>

It appears, then, that one might be able to derive much qualitative information about the nature of the electronic structure of a particular carbon in a relatively complicated molecule, due to the sensitivity of the carbon-13 chemical shift to minor changes in its electronic environment.

## CONFORMATIONAL ANALYSIS

Buchanon, Ross, and Stothers<sup>52</sup> have utilized  $\delta^{13}\text{C}$  as a sensitive probe in conformational analysis. The chemical shifts of the carbinol carbons of the cis- and trans-4-*t*-butylcyclohexanols (6 and 7) differ by 4.9 ppm, with the chemical shift of the trans isomer (7) 121.5 ppm from  $\text{CS}_2$ . Assuming that the chemical shift of



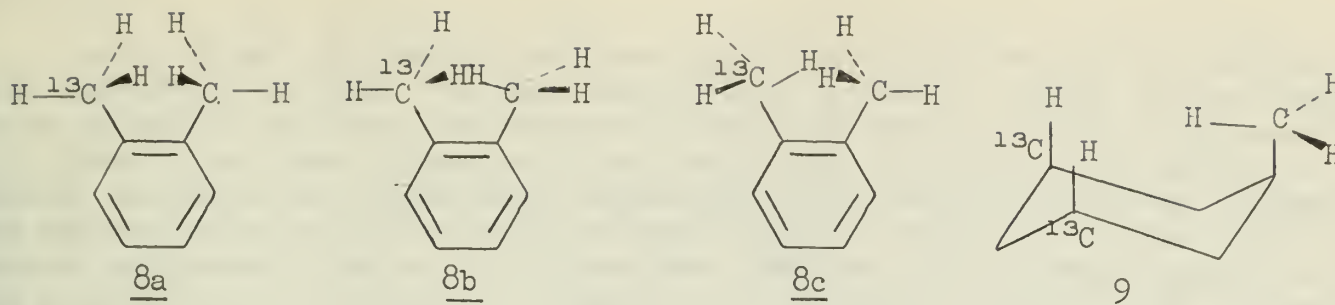
122.8 ppm for the carbinol carbon of cyclohexanol provides a measure of the relative populations of the two available chair formations, Stothers and coworkers calculated that cyclohexanol exists 74% in the equatorial form. This leads to a  $-\Delta G^\circ = 0.6$  kcal/mole, which is in the range found from proton nmr studies.<sup>53</sup> The  $\pm 0.3$  ppm error limit in  $\delta^{13}\text{C}$ , inherent in the dispersion mode technique used, would lead to error limits in  $\Delta G^\circ$  of  $\pm 0.4$  kcal/mole, although in principle one could obtain quite meaningful values of  $\Delta G^\circ$  by operating in the absorption mode.

An example of the precision possible in measuring  $\delta^{13}\text{C}$  is seen in the work of Woolfenden and Grant.<sup>54</sup> These workers measured the  $^{13}\text{C}$  chemical shifts of all the methylbenzenes, using complete proton decoupling, with an accuracy of 0.05 to 0.07 ppm. Postulating that only three conformations ( $\delta_{\text{a-c}}$ ), the most important of which is  $\delta_{\text{a}}$ , appreciably affect the  $^{13}\text{C}$  chemical shift, the observed  $\delta^{13}\text{C}$  for the methyls of all the compounds studied could be rationalized using the shift of toluene as a basis. Relative contributions of  $\delta_{\text{a-c}}$  were determined by a regression analysis of the empirical shifts, while a semitheoretical treatment of nonbonded repulsion energies between adjacent methyls yielded results consistent with the conformational postulates.<sup>54</sup>

The results for the methylbenzenes were particularly significant, since the ring







carbons restrict the methyls to conformations which are relatively easy to analyze.

Dalling and Grant<sup>55</sup> have extended the  $\delta^{13}\text{C}$  dependence on molecular structural features to the methylcyclohexanes, whose conformations have been extensively studied and characterized.<sup>53</sup> The observed  $\delta^{13}\text{C}$  of ring atoms could be correlated by a least squares analysis with nine parameters, all involving the effects of proximate methyl substituents on  $\delta^{13}\text{C}$ , in qualitative agreement with valence bond calculations.<sup>45</sup>

A relatively large chemical shift perturbation was observed<sup>55</sup> for the ring carbons  $\gamma$  to an axial methyl group (9), presumably resulting from a gauche interaction between the methyl hydrogens at C-1 and axial hydrogens at C-3 and C-5. One can see an analogy between this interaction in 9 and that observed in the methylbenzenes (8a-c). Grant and Cheney<sup>56</sup> have concluded that the conformational parameters involved in 8a-c and 9 can all be explained on the basis of steric interactions existing between proximate hydrogens on two sterically perturbed groups. In support of this, a calculation of the force component along the H- $^{13}\text{C}$  bond for 8a-c and 9, assuming only nonbonded hydrogen-hydrogen repulsive interactions, gave values which have a linear relationship with the observed  $^{13}\text{C}$  chemical shifts.

#### ELECTRONIC STRUCTURE-CARBANIONS

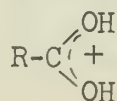
Waack, Doran, Baker, and Olah<sup>57</sup> have studied the  $^{13}\text{C}$  nmr spectra of  $\alpha$ - $^{13}\text{C}$ -enriched benzyllithium, diphenyllithium, and triphenyllithium in THF using the INDOR technique. They concluded that these species are substantially  $\text{sp}^2$ -hybridized on the basis of the 30-40 ppm deshielding of the  $\alpha$ - $^{13}\text{C}$  in the lithium derivatives relative to the corresponding hydrocarbons (Table 6). Since  $\text{sp}^2$ -hybridized carbons are generally found about 100 ppm downfield from  $\text{sp}^3$ -hybridized carbons, the 60-70 ppm discrepancy was attributed to the shielding the  $\alpha$ - $^{13}\text{C}$  would experience as a carbanion. Moreover, they concluded that the change in  $J_{^{13}\text{C-H}}$  in going from the hydrocarbon to the lithium derivative is consistent with a change in hybridization of  $\text{sp}^3$  to  $\text{sp}^2$  (Table 6).

Table 6.  $^{13}\text{C}$  Chemical Shifts and  $^1\text{H}$ -Proton Coupling Constants for Phenylmethylolithiums and Phenylmethanes<sup>57</sup>

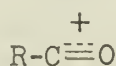
Compound	Solvent	$\delta^{13}\text{C}$ (ppm relative to $\text{CS}_2$ )	$J^{13}\text{C-H}$ (Hz)
$\Phi_3\text{CLi}$	THF	102	---
$\Phi_3\text{CH}$	$\text{CDCl}_3$	132	107
$\Phi_2\text{CHLi}$	THF	114	142
$\Phi_2\text{CH}_2$	$\text{CDCl}_3$	157	126
$\Phi\text{CH}_2\text{Li}$	THF	163	133
$\Phi\text{CH}_3$	Neat	172	126

#### OXOCARBONIUM AND CARBOXONIUM IONS

$^{13}\text{C}$  nmr spectroscopy has been instrumental in providing evidence for the existence and nature of stable carboxonium (10) and oxocarbonium (11) ions in strongly acidic solutions.<sup>13b</sup> Its specific application, along with other compelling evidence, will be extensively discussed in another seminar<sup>58</sup> and will not be covered here.



10



11





## CONCLUSION

Carbon-13 nmr spectroscopy has been applied to a wide variety of chemical problems with substantial success. In some instances it is used to supply unique information, while in others it is employed to corroborate data obtained by other physical methods.

There is no longer a technological barrier to the study of  $^{13}\text{C}$  spectra in natural abundance, as dramatically emphasized by the work of Grant and Litchman,<sup>21</sup> and Weigert and Roberts<sup>18</sup> on carbon-carbon coupling constants in their 0.02 to 0.04% natural abundance. The use of  $^{13}\text{C}$ -enriched compounds has important applications in the elucidation of biosynthetic pathways<sup>59</sup> and dilution studies,<sup>60</sup> and will probably increase.

Much molecular structural information is buried in  $^{13}\text{C}$  chemical shifts and coupling constants, and future work, as well as providing additional empirical data, will certainly focus on extracting meaningful information from these carbon-13 nmr parameters on a more sophisticated basis.

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## THE MECHANISM OF ELECTROPHILIC SUBSTITUTION OF PYRIDINES

Reported by Thomas R. Keenan

April 18, 1968

## INTRODUCTION

The mechanism of electrophilic substitutions of pyridines is not as well understood as that of benzene derivatives.<sup>1,2</sup> Qualitative observations indicate that these reactions of heteroaromatic compounds require more vigorous conditions to obtain satisfactory yields<sup>3,4</sup> but data have only recently become available which will help decide whether this is due to (a) the low reactivity of the conjugate acid or (b) the small amount of free base present under strongly acidic conditions. Presumably, when the nature of the reactive species is established, the quantitative effects of the ring nitrogen can be studied by comparing data for the correspondingly substituted benzene derivative. To do this sensibly it must be established if the mechanism of electrophilic substitution is the same for corresponding homo- and heteroaromatic compounds. The purpose of this seminar is to examine the quantitative data which are available concerning the mechanism of acid-catalyzed hydrogen exchange and nitration of pyridines and pyridine N-oxides. Of particular interest will be the factors determining whether the conjugate acid or the free base is the reactive substrate.

## ACID-CATALYZED HYDROGEN EXCHANGE IN PYRIDINES

Nearly all of the data which are available concerning electrophilic hydrogen exchange and nitration of pyridines were obtained from reactions run in concentrated sulfuric acid or oleum solution. In order to get an accurate estimate of the relative amounts of the conjugate acid and the free base present under these strongly acidic conditions, it is necessary to know the acidity function which pyridines follow. Katritzky and coworkers<sup>5</sup> used a spectrophotometric method to determine that substituted pyridines follow the Hammett acidity function,<sup>6</sup>  $H_0$ , over the range pH 1 to  $H_0$  -6.5. This function will be appropriate, therefore, for pyridines similar to those tested.

Katritzky and Ridgewell have studied hydrogen-tritium exchange in 2,6-dimethylpyridine, (1), and 2,4,6-trimethylpyridine, (2), in strongly acidic tritiated sulfuric acid and have compared their results with those obtained for bis-1,2,4,6-tetramethylpyridinium sulfate, (3).<sup>7</sup> They found that the reaction was first order in substrate and that only the 3- and 5-positions in each compound exchanged at a measurable rate. In addition, they found that the 1,2,4,6-tetramethylpyridinium ion reacted with a comparable but faster rate than did 2,4,6-trimethylpyridine and that all three compounds showed parallel rate dependences on acidity, (Fig. 1). They interpreted these data as indicating that the reactive species is the conjugate acid;

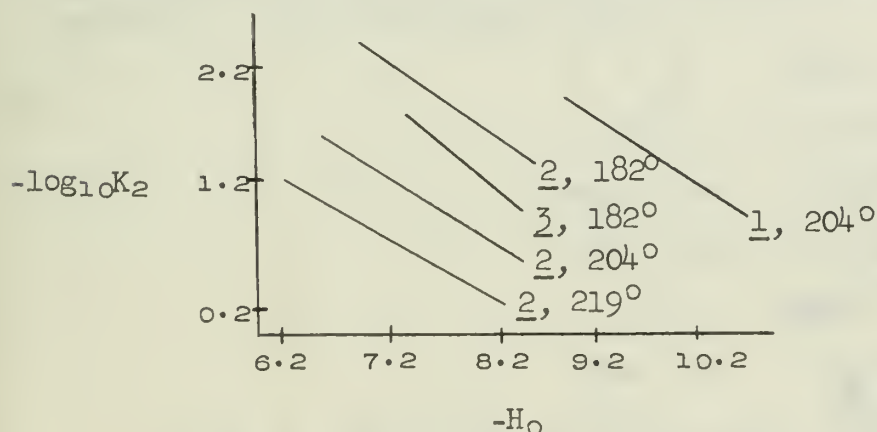
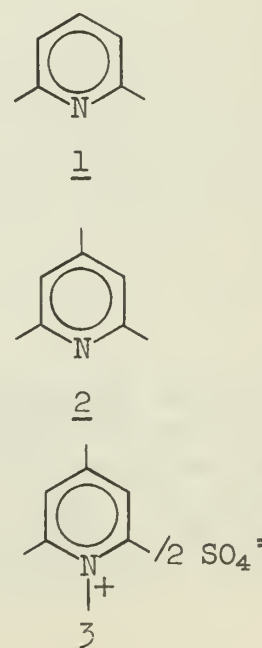


Figure 1. Plots of  $-\log_{10} k_2$  vs.  $-H_0$  for 2,6-dimethylpyridine (1), 2,4,6-trimethylpyridine (2), and 1,2,4,6-tetramethylpyridinium sulfate (3).

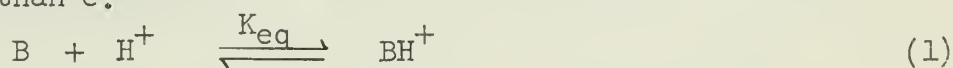




the faster rate of the N-methyl compound was expected. They also reasoned that parallel acidity dependence of the rate would not be expected for reaction via the free base, since the concentration of free base would vary by several powers of ten over the acidity range studied while the concentration of N-methyl compound would remain constant. A study of the temperature dependence of the rate of reaction of 1 and 2 gave values for the entropy of activation,  $\Delta S^\ddagger$ , in the range of -35 to -65 e.u. These large negative values of  $\Delta S^\ddagger$  were interpreted as reflecting greater order in the transition state; greater solvation of the doubly charged transition-complex than the solvation of the individual ions would seem plausible.<sup>7-9</sup> Finally, they determined that unreasonably large values (ca.  $10^{25}$ ) for the Arrhenius frequency factor, A, would be required if the reaction were proceeding via the unprotonated species.<sup>7</sup>

Having secured this evidence indicating that the reactive species for hydrogen exchange is the conjugate acid in these compounds, Katritzky attempted to compare rates of hydrogen exchange of the correspondingly substituted benzene derivative. The substitution of  $=NH^+$  for  $=CH-$  in benzene was found to decrease the rate of hydrogen exchange in the meta-position by a factor of ca.  $10^{18}$ . To obtain this value, however, considerable extrapolation of rate data was required and the possible variation of the  $H_0$  scale with temperature had to be neglected. The factor of  $10^{18}$  must be considered as a rough estimate, therefore, in the absence of data which will extend the known temperature range of  $H_0$ .

A common method for determining whether a species is reacting via the free base or the conjugate acid is the examination of the variation of a calculated unimolecular rate constant with acidity.<sup>10</sup> For the case of acid-catalyzed hydrogen exchange in pyridines, if  $K_{eq}$  is the equilibrium constant for nitrogen protonation (Eq. 1), then the concentration of the conjugate acid is represented by Equation 2. If it is assumed that carbon protonation is the rate limiting step, then reaction of the conjugate acid would be represented by Equation 3, where  $k_A$  is a constant. If a unimolecular rate constant,  $k_2$ , is calculated using the total amount of added base,  $B_0$ , (Eq. 4), it follows that  $k_2$  is represented by Equation 5 and is a linear function of hydrogen ion concentration. A plot of  $\log(k_2)$  versus  $-H_0$  will give a straight line of unit slope. If reaction via the free base is assumed, it can be shown that the rate is represented by Equation 6, where  $k_B$  is a constant. A plot of  $\log(k_2)$  vs.  $-H_0$  for this case will give a straight line of zero slope. These simplified considerations have been used by Katritzky in the study of acid catalyzed deuterium incorporation into the ring of several aminopyridines by nmr.<sup>10</sup> Here the reactive species may be the free base, the first conjugate acid, or the second conjugate acid. An idealized rate profile was derived (Fig. 2) where exchange of the free base is assumed over the portion of the curve a-b-c, exchange of the first conjugate acid is assumed over the portion c-d-e, and exchange on the diprotonated substrate is assumed at acidities higher than e.



$$(BH^+) = K_{eq}(B)(H^+) \quad (2)$$

$$\text{obs. rate} = k_A(BH^+)(H^+) \quad (3)$$

$$\text{obs. rate} = k_2(B) \quad (4)$$

$$k_2 = \frac{k_A}{K_{eq}}(H^+) \quad (5)$$

$$\text{obs. rate} = \frac{k_B}{K_{eq}}(B)(H^+) \quad (6)$$

A plot of  $\log(k_2)$  vs.  $-H_0$  for hydrogen exchange of 4-aminopyridine at  $107^\circ$  gave a slope of ca. +0.5 over the range  $H_0 = 0$  to  $-6$  and a slope of ca. -0.4 was found at acidities greater than  $H_0 = -6$ . These data were interpreted as representing the portion c-d-e of Figure 2, i.e. reaction of the first conjugate acid. The negative slope was said to represent the difference between the acidity functions for carbon- and nitrogen-protonation.<sup>10</sup> The rate profile for 2-amino-5-methylpyridine at  $107^\circ$







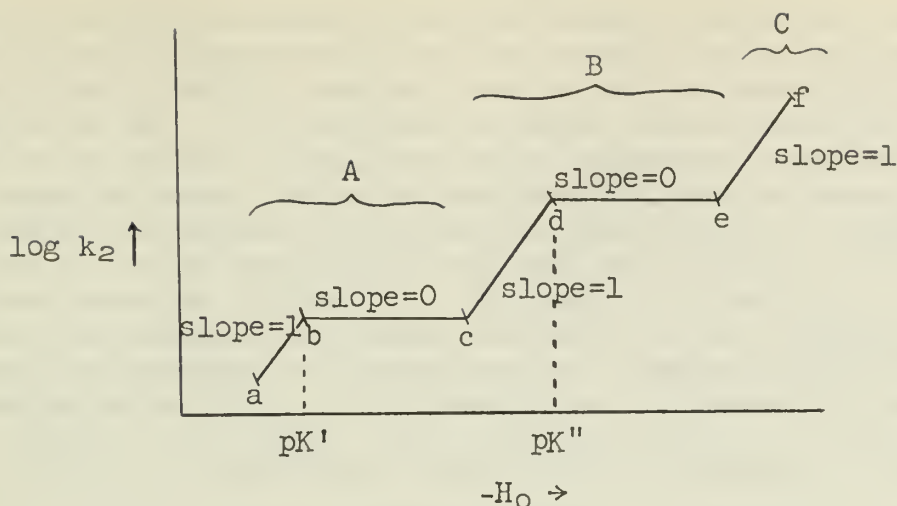


Figure 2. Idealized rate profile  
for acid-catalyzed hydrogen exchange in aminopyridines.

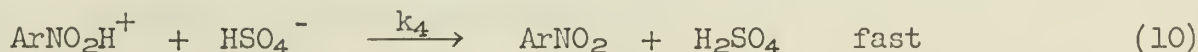
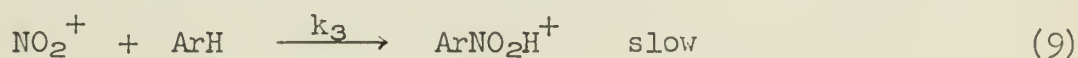
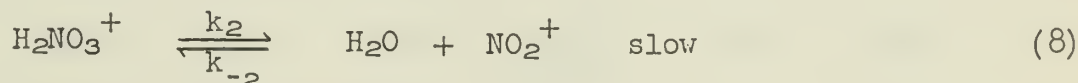
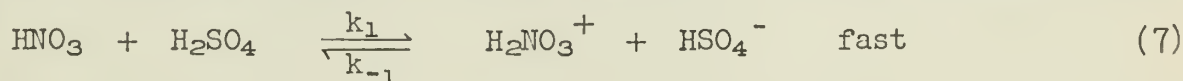
A: free base; B: first conjugate acid; C: second conjugate acid

gave a straight line of slope +0.64 over the range  $H_0 = -2$  to  $-6$ , which was interpreted as representing reaction via the first conjugate acid (c-d of Fig. 2). The rate profile for 4-amino-2,6-dichloropyridine at  $107^\circ$  gave a near-zero negative slope over the range  $H_0 = -1$  to  $-4$  and a positive change in the slope to ca. +1 was observed at higher acidities. The acidity range studied was not extended appreciably above  $H_0 = -4$ , however, so an accurate determination of the slope in this region was not possible. These data were interpreted as representing portion b-c-d of Figure 2. A changeover of mechanism from reaction of the free base to reaction of the first conjugate acid was said to be occurring at an  $H_0$  of about  $-4$ .<sup>10</sup>

These experimental data do not clearly support the theory and it seems that some of the assumptions which were made are not justified. This treatment requires that the acidity function for carbon-, ring nitrogen-, and amino nitrogen-protonation must all be the same. Little data are available which will cast light on the appropriate acidity function for carbon protonation in pyridines, but Arnett and Mach<sup>11</sup> have found that substituted dimethylanilines do not follow  $H_0$ . To the extent that protonation of the amino group on pyridines resembles protonation of dimethylanilines,  $H_0$  will not be followed. Also, the presence of the amino group may alter the structure of pyridine sufficiently that protonation of the ring nitrogen will not follow  $H_0$ . Two basic centers in the molecule may increase significantly the importance of hydrogen-bonded complexes,  $Ar \cdot H_2SO_4$ , (a dipolar species with a strong positive pole on the aromatic compound) such as those proposed for benzenes.<sup>12</sup> Changes in solvent polarity, solvating power, and salt effects with changes in acidity may also be complicating factors.<sup>9</sup>

#### NITRATION OF PYRIDINES

The mechanism of nitration of benzenes in sulfuric acid solution is best represented by Equations 7-10.<sup>9</sup> The rate of nitration may be controlled by either or both of the slow steps, Equations 8 and 9. It is known, however, that the conversion of nitric acid to  $NO_2^+$  is virtually complete at acidities greater than



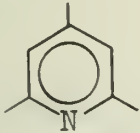
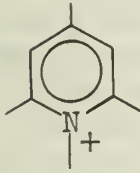
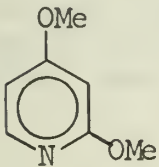
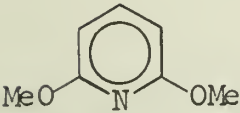
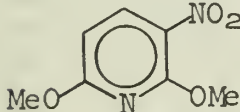
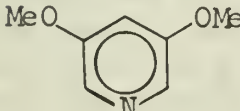
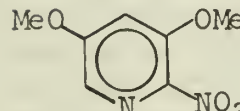
90%  $H_2SO_4$ .<sup>9</sup> In the nitration of pyridines,  $NO_2^+$  is generally assumed to be the nitrating species and Equations 7 and 8 will presumably apply to this mechanism as



well. Thus at acidities greater than 90%  $\text{H}_2\text{SO}_4$ , the initial concentration of  $\text{NO}_2^+$  can be unambiguously determined from the amount of added nitric acid and a consideration of the aromatic reactive species will be uncomplicated by a changing concentration of  $\text{NO}_2^+$ . In solutions of lower acidity than 90% sulfuric acid, the changes in concentration of  $\text{NO}_2^+$  may be an important complicating factor.

The strong evidence that acid-catalyzed hydrogen exchange proceeds via the conjugate acid of methylated pyridines led Katritzky and coworkers to investigate the nitration of these compounds in sulfuric acid solution.<sup>13-15</sup> Some of the available data are presented in Table 1. The rate of nitration of 2,4,6-trimethylpyridine and its 1-methyl derivative were shown to be comparable and to have roughly parallel acid dependencies in oleum solution. Unfortunately, the 1-methyl compound was not studied in sulfuric acid solution, so the range of comparison of the two

Table 1. Nitration of Pyridines in Sulfuric Acid Solution

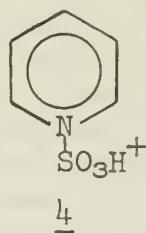
Compound	$\text{pK}_a$	Temp. °C	$\text{H}_0$	$\log_{10} k_2$	$\log A$	$\Delta S^\ddagger$	$E_a$
	6.5	101.3	-8.9	-3.005	7.39	-26.7	17.7
	--	101.3	-10.6	-3.836	--	--	--
	4.5	25.0	-8.84	-1.89	9.48	--	15.5
	1.60	22.5	-8.99	-0.84	8.95	-18.2	13.1
	-3.86	36.9	-8.89	1.91* -3.12	15.86*	+12.4* -10.4	19.7
	4.44	22.6	-8.90	-8.11	8.84	-20.0	12.4
	-2.52	39.9	-8.99	2.18* -3.62	17.5*	+15.9*	22.7

\*Corrected values assuming reaction of the free base.





compounds is small. In addition, Katritzky did not rule out the possibility of formation of N-sulfonic acids (Structure 4) in oleum solution. It may be that the



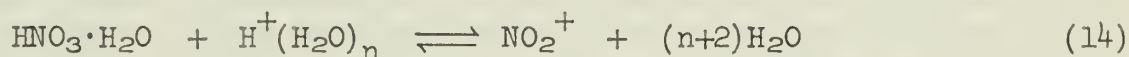
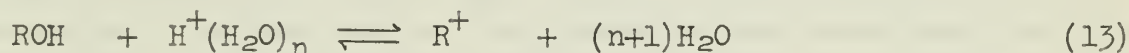
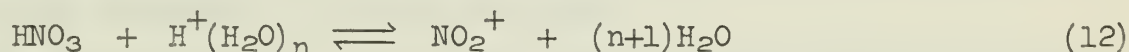
effect of the N-SO<sub>3</sub>H<sup>+</sup> group on the rate of nitration is similar to that of N-CH<sub>3</sub><sup>+</sup>, thus accounting for parallel acidity dependence.

Katritzky has found additional evidence that the conjugate acid is the reactive species from calculated maximum rates of reaction (diffusion control) of the free base and NO<sub>2</sub><sup>+</sup> using the encounter rate, Equation 11, where  $\delta$  is the viscosity of

$$k_2(\text{encounter}) = \frac{kT}{3\delta} \frac{(r_A - r_B)^2}{r_A r_B} \cdot \frac{N}{1000} \quad (11)$$

the medium,  $k$  is Boltzman's constant and  $r_A$  and  $r_B$  are the radii of the acid and base. Using appropriate values for these constants and the appropriate  $pK_a$  for compound 2, they calculated that the required rate of reaction of the free base in 98% H<sub>2</sub>SO<sub>4</sub> would be 100 times faster than diffusion control. That is, less than 1% of the observed rate can be accounted for by reaction via the free base even if zero activation energy is assumed for its reaction with NO<sub>2</sub><sup>+</sup>.

Nitration studies of quinoline<sup>16,17</sup> and isoquinoline<sup>16</sup> and their N-methyl perchlorates<sup>16</sup> in 71-98% sulfuric acid indicate that the reactive species in these compounds is the conjugate acid. Schofield observed that the dissociation of nitric acid to give nitronium ion, Equation 12, was formally similar to the ionization equilibria of triaryl carbinols, Equation 13.<sup>16</sup> He reasoned that if these equilibria are alike, they should have parallel acidity functions. Since the nitric acid



molecule is present as its monohydrate over the acidity range studied, the acidity function  $H_R + \log(a_{\text{H}_2\text{O}})$  was assumed to apply where  $H_R$  is the acidity function for triaryl carbonols and  $a_{\text{H}_2\text{O}}$  is the activity of water at a given sulfuric acid concentration (Eq. 8). These considerations led to the accurate prediction that a plot of the logarithm of the observed second order rate constant ( $\log k_{2\text{obs}}$ ) versus  $-(H_R + \log(a_{\text{H}_2\text{O}}))$  should give a straight line of unit slope if the conjugate acid is the reacting species.<sup>16</sup> These plots for quinoline, isoquinoline and their N-methyl derivatives did indeed give the predicted results in the range 71-84% H<sub>2</sub>SO<sub>4</sub>. Inherent in these predictions, however, is the assumption that the attack of nitronium ion on the aromatic substrate is the rate limiting step. The possibility that the forward reaction in Equation 14 is the limiting step is not rigorously excluded by these data. Parallel acidity dependence for the nitration of the N-methyl and unsubstituted quinolines may not indicate that nitration is proceeding on the conjugate acid if the nitration of each species is much faster than the rate of formation of NO<sub>2</sub><sup>+</sup>. Ridd<sup>17</sup> found that at acid concentrations above 90% H<sub>2</sub>SO<sub>4</sub>, where conversion of HNO<sub>3</sub> to NO<sub>2</sub><sup>+</sup> is complete, the dependence of the rate of reaction of quinoline on acidity was parallel to that of the nitration of the trimethylanilinium ion. He interpreted these results as indicating that the conjugate acid is the reacting species. No studies of N-methyl quinoline have been carried out at acidities greater than 90% H<sub>2</sub>SO<sub>4</sub>.

As the basicity of pyridine is decreased by appropriate substitutions, the





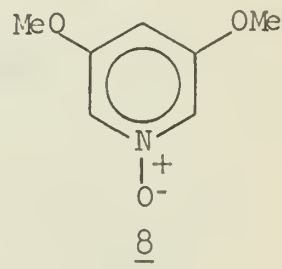
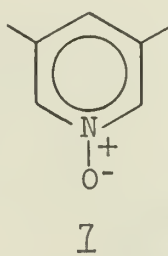
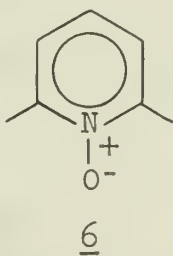
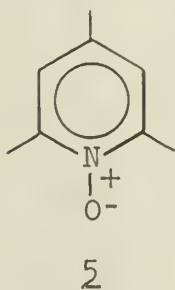
concentration of the free base under typical nitrating conditions will increase. Katritzky reasoned that if a suitably weakly basic pyridine could be found, nitration via the free base might be observed. Accordingly, the first and second nitrations of 2,6-dimethoxypyridine were studied (Table 1).<sup>14</sup> The shape of the rate profile for nitration of 2,6-dimethoxypyridine ( $pK_a = 1.60$ ) was termed appropriate for reaction via the conjugate acid and the entropy of activation ( $\Delta S^\ddagger = -18.2$  e.u.) was consistent with this observation. The rate of nitration of the 3-nitro derivative ( $pK_a = -3.86$ ) was a sensitive function of acidity below  $H_0 = -9$ , however, and a plot of  $\log(k_2)$  vs.  $-H_0$  was approximately linear with a negative unit slope. These data were termed consistent with nitration via the free base and a value for the entropy of activation after correction for the concentration of the free base was positive ( $\Delta S^\ddagger = +12.4$ ).<sup>14</sup> The conclusion that the reaction is proceeding on the unprotonated species is based entirely on the shape of the rate profile plot, however, since positive entropies of activation can be calculated from "corrected" rates of reaction for any of these compounds if reaction via the free base is assumed. Application of the encounter rate criterion indicates that reaction could be proceeding on either or both species.<sup>14</sup> Katritzky found similar results for the nitration of 3,5-dimethoxypyridine ( $pK_a = 4.44$ ) and its 2-nitro derivative ( $pK_a = -2.52$ ) (Table 1). Here the encounter rate criterion ruled out reaction of the free base in the first nitration and his conclusion that the second nitration is proceeding on the unprotonated species is based entirely on the shape of the rate profile plot.

The data which are available for pyridines indicate that the reactive species is determined by the  $pK_a$  of the base. At low acidities the concentration of free base is high but the rate of reaction is determined by equilibria involving the formation of  $NO_2^+$ . At higher acidities the concentrations of both  $NO_2^+$  and  $ArH^+$  increase and eventually become the predominating reactive species. Nitration on the free base can be observed, therefore, only for the most weakly basic pyridines. Katritzky has summarized these observations with the following rules for nitration of pyridines in sulfuric acid solution: "(a) basic pyridines ( $pK_a > +1$ ) will be nitrated as cations only...[and] (b) very weakly basic pyridines ( $pK_a < -2.5$ ) undergo nitration as the free bases..."<sup>15</sup> These rules seem justifiable for pyridines.

#### ACID-CATALYZED HYDROGEN EXCHANGE IN PYRIDINE N-OXIDES

Pyridine N-oxides are generally weaker bases than the corresponding pyridines and at low acidities hydrogen exchange may be complicated by base-catalyzed deprotonation.<sup>18,19</sup> There is recent indication that oxygen protonation does not follow the Hammett acidity function for these compounds and the amide acidity function,  $H_A$ ,<sup>20,21</sup> provides better correlation with the ratio of free base to conjugate acid at a given concentration of sulfuric acid.<sup>22</sup> Nevertheless, most results<sup>23,24</sup> are reported in terms of  $H_0$  and conclusions based on them may require appropriate qualification.

Katritzky<sup>23,24</sup> has investigated the rate of deuterium incorporation into the various ring positions of several substituted pyridine N-oxides in deuteriosulfuric acid by nmr. 2,4,6-Trimethylpyridine-1-oxide, 5, and 2,6-dimethylpyridine-1-oxide, 6, were found to undergo hydrogen exchange in the 3- and 5-positions; the latter



compound decomposed slowly during the reaction, precluding establishment of accurate data. However, the rates of exchange (unreported for 6) were said to be comparable, thus indicating reaction on species of the same charge type.<sup>24</sup> The rate profile for the trimethyl derivative, 5, ( $\log(k_2)$  vs.  $-H_0$ ) gave a straight line with a slope of  $+0.33$  over the range  $H_0 = -3$  to  $-8$ . The entropy of activation for this process was





said to be appropriate for reaction via the conjugate acid, but no value was reported.<sup>24</sup> The slope of the rate profile plot was interpreted as evidence that the reactive species was the conjugate acid since a slope of zero would be expected for a species whose concentration was being reduced significantly with increasing acidity. It does not appear, however, that these data rule out reaction via the free base since other solvent effects could well account for the observed slope. It was not possible to use the rate of quaternary salt exchange as a mechanistic criterion for this case because the N-methoxy derivative decomposed under the reaction conditions.

Hydrogen exchange in the 2-, 4-, and 6-positions has been observed in 3,5-dimethylpyridine-1-oxide, 7.<sup>24</sup> The slope of the rate profile plot over the range  $H_0 = 0$  to  $-8$  was linear with a slope of  $-0.13$ . These results were interpreted as indicating exchange on the free base; the increase in acid concentration being compensated for by a decreasing concentration of free base, thus giving little change in the bimolecular rate constant over a large change in acidity. A large increase in the rate of exchange at lower acidities was thought to be due to base-catalyzed deprotonation. A complicated curve was obtained for the rate profile of hydrogen exchange in the 2-position of 3,5-dimethoxypyridine-1-oxide, 8, over the range  $pH = 3$  to  $H_0 = -5$ .<sup>24</sup> The observed slopes did not correspond exactly to any region of Figure 2 and no correction has been made which takes into account the appropriate acidity function,  $H_A$ .

These results, although not conclusive, indicate that different factors are important in exchange at the 3- and 5-positions compared to the 2-, 4-, and 6-positions of pyridine N-oxides. It seems premature, however, to assign the reason for these differences to reaction via the conjugate acid in one instance and via the free base in another, even though these are the most common explanations.<sup>23,24</sup>

#### NITRATION OF PYRIDINE N-OXIDES

The nitrations of pyridine N-oxides have been important synthetic reactions for many years since these reactions proceed under much milder conditions and in better yields than do the nitrations of the corresponding pyridines.<sup>25</sup> Mechanistic studies were complicated by the high reactivity of these compounds; convenient rates of nitration were generally found at sulfuric acid concentrations lower than 90%. At these acidities, the observed rates of nitration may have only represented rate limiting formation of  $NO_2^+$ . Unfortunately, this complicating factor appears not to have been recognized by most of the workers in this field and only a brief footnote in the latest paper<sup>26</sup> can be found which considers this possibility. Very little rate data are available for acidities greater than 90%  $H_2SO_4$ .

Some of the available data for nitration of pyridine N-oxides are presented in Table 2.<sup>26-28</sup> The results indicate that nitration of pyridine-1-oxide is likely to

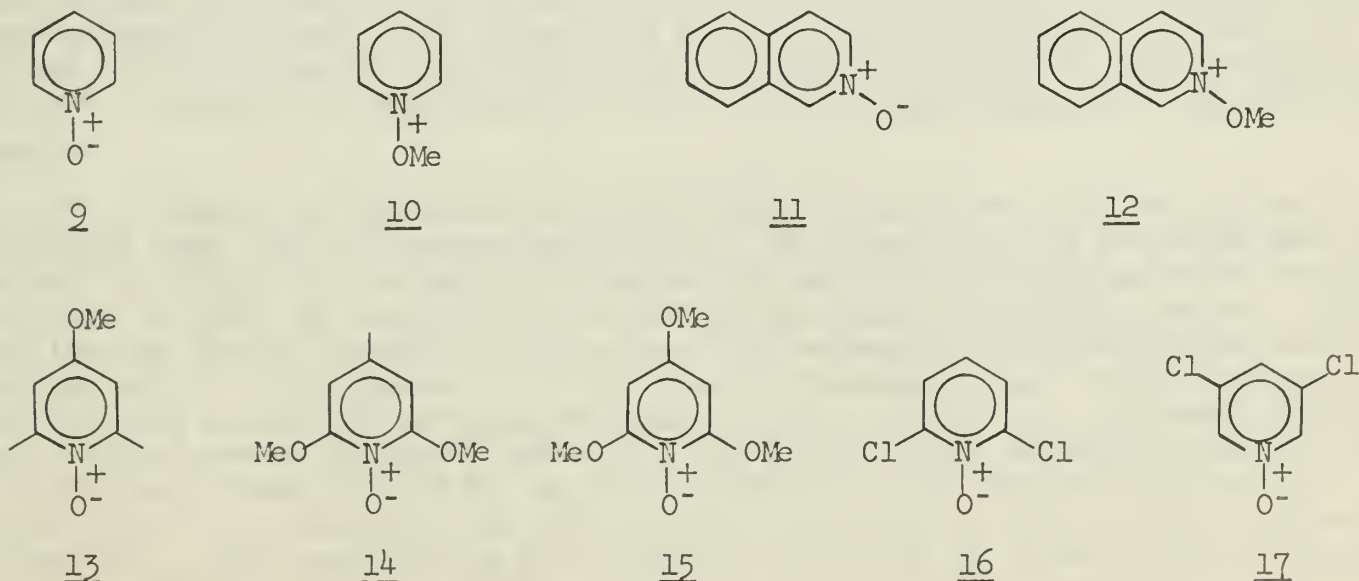




Table 2. Nitration of Pyridine N-Oxides in Sulfuric Acid Solution

Compound	Temp. °C	H <sub>0</sub>	log <sub>10</sub> K <sub>2</sub>	log A	ΔS <sup>‡</sup> e.u.	E <sub>a</sub> kcal/mole
<u>9</u>	25	-8.16	-7.44	9.8	-15.8	23.5
<u>10</u>	125	-8.0	< -6	--	--	--
<u>11</u>	25	-7.8	-3.48	8.3	-22.7	14.7
<u>12</u>	25	-7.8	-3.97	8.4	-22.2	15.5
<u>6</u>	25	-8.5	-5.98	10.8	--	22.9
<u>13</u>	24.8	-9.0	-2.84	9.1	-18.5	16.6
<u>14</u>	25	-8.2	-3.09	6.9	-26.1	14.5
<u>15</u>	26	-7.5	-2.92	9.5	-17.2	16.9
<u>8</u>	49	-7.7	-3.23	10.5	-12.3	20.3
<u>7</u>	81	-9.3	-4.70*	19.0*	26.3* -15.1	25.3
<u>16</u>	84	-9.9	0.346*	13.8*	2.7* -14.2	23.5
<u>17</u>	83.8	-8.9	-0.165	14.1*	15.1* -7.2	27.9

\*Corrected values assuming reaction of the free base.

proceed via the free base since nitration of its N-methoxy derivative could not be effected under conditions where pyridine-1-oxide was easily nitrated. The N-oxide of isoquinoline was found to undergo nitration with a rate and acid dependence similar to its N-methoxy derivative.<sup>28</sup> These results may indicate reaction via the conjugate acid is operative or that formation of nitronium ion is rate limiting. If the latter is correct, the calculated Arrhenius parameters represent the formation of NO<sub>2</sub><sup>+</sup> and not the reaction of substrate with nitronium ion. Rate profile plots for compounds 6, 8, and 13-15 indicate that reaction is proceeding on the conjugate acid in the 3-position. Nitration in the 4-position of compounds 7, 16, and 17 are said to proceed via the free base.<sup>26,28</sup> Katritzky has generalized these results by stating that nitration in the β-position of pyridine N-oxides occurs on the conjugate acid and the free base is the reactive species for γ-nitration. α-Nitration of 3,5-dimethoxypyridine-1-oxide, 8, appears to proceed via the conjugate acid but the entropy of activation is less negative than would be expected.<sup>26</sup> The low basicity of these compounds made application of the encounter rate criterion inconclusive.<sup>26</sup>

#### SUMMARY

The mechanism of electrophilic substitution in pyridines remains less well understood than that of benzene derivatives. The details of the mechanism have been assumed to be the same as those of benzenes and most of the experiments in this area have been designed to elucidate the nature of the organic reactive species. Major complicating factors appear to have arisen from assumptions concerning the rate limiting step in this process. Also, it has been assumed that other electrophilic substitutions proceed by the same mechanism as does nitration. Apparently additional work in this area is necessary before the validity of these assumptions can be tested. Of particular interest would be the determination of rate data for nitrations carried out in non-aqueous media with an appropriate nitronium salt (e.g. nitronium fluoborate). Here reaction via the conjugate acid would be ruled out and complicating factors concerning the rate limiting step would be less important.







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# STABLE CARBONIUM IONS: ACYLIUM IONS AND PROTONATED CARBOXYLIC ACIDS

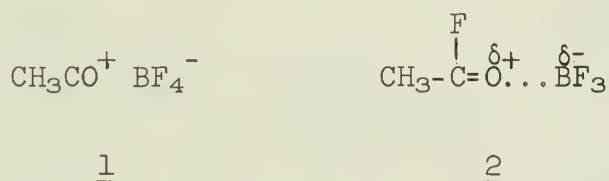
Reported by C. Robert Payet

April 22, 1968

For many years acylium ions ( $R-CO^+$ ), or oxocarbonium ions, were intuitively considered to be intermediates in Friedel-Crafts reactions. During the last twenty-five years the existence of these oxocarbonium ions has been shown by the results of a variety of investigations. This seminar will present evidence indicating their formation from both acyl fluorides and protonated carboxylic acids. Since 1960 both the site of proton attack and the stereochemistry of these protonated acids have been determined, and these results will be discussed.

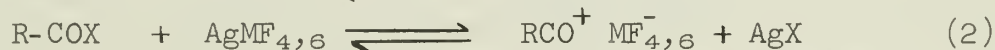
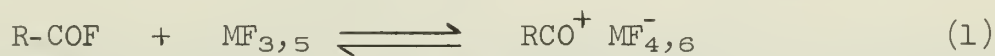
## ACYLIUM IONS FROM ACYL FLUORIDES

In 1943 F. Seel<sup>1</sup> reacted acetyl fluoride and boron trifluoride at  $-50^\circ$  to produce the first isolated oxocarbonium salt (1). Data from conductivity measurements demonstrated that the 1:1 adduct was ionic in liquid  $SO_2$  at  $-70^\circ$ , and the infrared studies of Susz and Wuhrmann<sup>2</sup> confirmed that the crystalline salt was predominantly ionic. Only a small amount of the donor-acceptor complex 2 was detected.



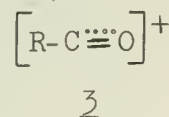
The ionic salt and donor-acceptor complex of the acetyl chloride-aluminum chloride adduct were differentiated by Cook<sup>3</sup> on the basis of their infrared carbonyl absorptions. Following these initial studies of the adducts of acyl halides and Lewis acids thorough investigations have been made with infrared and nuclear magnetic resonance (nmr) spectroscopy, X-ray diffraction, and chemical reactions.

Two principal methods have been employed to synthesize the oxocarbonium ion salts.<sup>4,5</sup> In the "fluoride method" (eqn. 1) the acyl fluoride and the Lewis acid metal fluoride are mixed in Freon 12 or 113 at temperatures ranging from 0 to  $-78^\circ$ . The "silver-salt method," used when the acyl fluorides are hard to obtain, involves the reaction of an acyl halide with the desired silver salt (eqn. 2). Because the  $SbF_5$  adducts are generally the most stable they have been most thoroughly investigated.



R = alkyl, aryl; M = B, As, P, Sb; X = Cl, Br

**INFRARED STUDIES.** From an investigation of the liquid acetyl chloride-aluminum chloride adduct Cook<sup>3</sup> found that the infrared band of the methyl oxocarbonium ion (3, R = methyl) was in the triple-bond region of the spectrum ( $2307\text{ cm}^{-1}$ ). Olah and his coworkers also found that the solid  $SbF_5$ -adducts exhibited a band in this region.<sup>4-9</sup> Primary adducts exhibited a strong band near  $2300\text{ cm}^{-1}$  which was assigned to the oxocarbonium ion 3 (see Table 1).<sup>4,5</sup> In the spectra of the secondary and tertiary acylium ions the corresponding band appeared at lower frequencies. This shift with increased branching was attributed to conjugation with the carbonyl moiety.<sup>6</sup> The low frequency of the phenyl oxocarbonium absorption was also attributed to conjugation of the phenyl ring with the carbonyl group.<sup>4</sup> (Table 1)

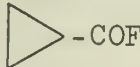
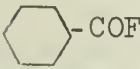


The *t*-butyl oxocarbonium-hexafluoroantimonate salt decomposed during the infrared investigations. A new peak, which could not be assigned to any pivalyl derivatives, to other acylium ions, or to the decomposition products (polyisobutylenes, CO, HF) appeared at  $2835\text{ cm}^{-1}$ . It was proposed that the new peak was due to the methyl stretch of the *t*-butyl cation (4). This conclusion was supported by the nmr



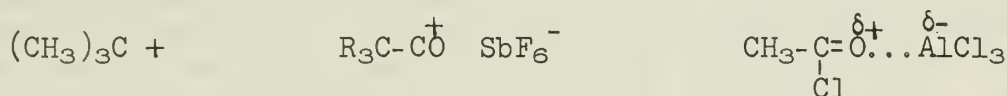


Table 1 : Infrared Stretching Frequencies ( $\text{cm}^{-1}$ ) of Acyl Fluorides and Their Adducts with Antimony Pentafluoride.<sup>a</sup>

Compound	Acyl Fluoride	SbF <sub>5</sub> Adduct		Reference
	$\nu_{\text{C=O}}$	$\nu_{\text{C=O}}$	$\nu_{\text{C}=\text{O}^+}$	
CH <sub>3</sub> COF	1848vs	1621w 1554w	2294vs	4
CH <sub>3</sub> CH <sub>2</sub> COF	1845vs	1610m	2290vs	4
(CH <sub>3</sub> ) <sub>2</sub> CHCOF	1840vs	1585m	2270vs	6
(CH <sub>3</sub> ) <sub>3</sub> C-COF	1823vs	1570vs	2260vs	6
Ph-COF	1812vs	1531m	2212vs	4
CH <sub>2</sub> =CHCOF	1825		2250	9
Ph-CH=CHCOF	1805		2210	9
 -COF	1815		2225	7
 -COF	1835		2255	7
FOC-(CH <sub>2</sub> ) <sub>2</sub> -COF	1845, 1792	1810 1550, 1630	2300	8
FOC-(CH <sub>2</sub> ) <sub>3</sub> -COF	1842		2290	8

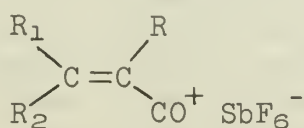
<sup>a</sup>vs, very strong, m, medium; w, weak.

data<sup>6</sup> and by the fact that pivalyl chloride was known to decarbonylate under Friedel-Crafts conditions.<sup>10,11</sup> Both the triethylacetyl- and triphenylacetyl oxocarbonium ions (5) lost carbon monoxide and hydrogen fluoride so quickly that their infrared spectra contained no carbonyl absorptions.

45 (R=Et, Ph)6

No bands that could be attributed to the carbonyl groups of the acyl fluorides were seen in the infrared spectra of any of the adducts.<sup>4-9</sup> When Cook<sup>3</sup> investigated the liquid acetyl chloride-aluminum chloride adduct he found a strong infrared band at  $1637 \text{ cm}^{-1}$  which he assigned to the donor-acceptor complex 6. In the spectra of the simple alkyl adducts which Olah and his coworkers<sup>4-6</sup> studied bands of medium to weak intensity were found in this region. Because the intensities of these peaks were much weaker than those near  $2300 \text{ cm}^{-1}$  it was concluded that the adducts were predominantly ionic. (Table 1). Later, however, it was reported<sup>7,9</sup> that no donor-acceptor bands appeared when extreme precautions to exclude water were made, and that adding traces of water caused the peaks to reappear. Water hydrolyzed the SbF<sub>5</sub> to hydroxyantimony fluorides which were weaker acids and coordinated with the oxygen instead of ionizing the acyl fluorides.

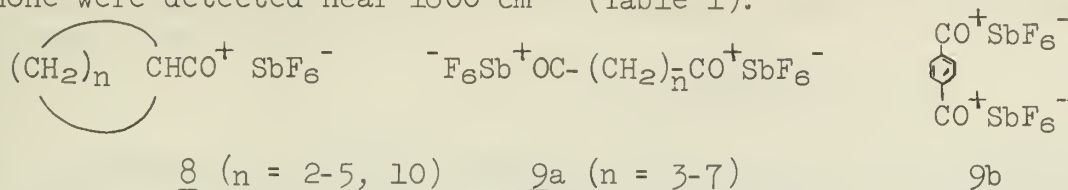
Olah and Comisarow<sup>9</sup> reported that the adducts of several  $\alpha,\beta$ -unsaturated fluorides (7) were completely ionic. The low frequency of the  $\text{C}=\text{O}^+$  absorption ( $2240 \text{ cm}^{-1}$ ) was attributed to conjugation of the carbonyl group with its adjacent double bond. (Table 1).

7

	R	R <sub>1</sub>	R <sub>2</sub>
a. acryloyl	H	H	H
b. methacryloyl	Me	H	H
c. crotonyl	H	Me	H
d. tigloyl	Me	Me	H
e. $\beta,\beta$ -dimethylacryloyl	H	Me	Me
f. cinnamoyl	H	Ph	H



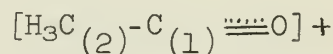
Olah and Comisarow<sup>7</sup> also found that all of the cycloalkyl adducts (8) which were examined were ionic. Strong infrared bands were seen in the 2200-2250  $\text{cm}^{-1}$  region, and none were detected near 1600  $\text{cm}^{-1}$  (Table 1).



All alkylene- and arylenediacyl fluoride adducts (9) that have been investigated exhibit infrared spectra characteristic of acylium ions.<sup>8</sup> The spectrum of the succinyl adduct, however, contained absorptions indicative of both an ionic salt and a donor-acceptor complex. A band at 1810  $\text{cm}^{-1}$  led Olah and Comisarow to conclude that an equilibrium between the free and complexed acyl fluoride was occurring at one end of the adduct. Both the oxalyl and malonyl adducts were too unstable to investigate, presumably because of charge-charge repulsion.

X-RAY STUDIES. Rasmussen and Broch<sup>12</sup> used X-ray diffraction to investigate the benzoyl chloride-aluminum chloride adduct and concluded that the aluminum atom was coordinated with the carbonyl oxygen atom by a 1.84-Å bond. They also reported that the bond angles and lengths of the benzoyl chloride were normal in the adduct.

From an X-ray study of the acetyl fluoride-antimony pentafluoride adduct Boer<sup>13</sup> concluded that it was an ionic salt. The small  $\text{C}_1\text{-C}_2$  bond distance (1.378 Å), which was shorter than that in the isoelectronic acetonitrile (1.458 Å), was attributed to positive charge on  $\text{C}_1$  in 10. The  $\text{C}_1\text{-O}$  distance (1.116 Å) was close to the  $\text{C}\equiv\text{O}$  bond in carbon monoxide (1.128 Å) and shorter than that in normal ketones and aldehydes (1.2 Å). A molecular orbital calculation, which indicated a net Mulliken charge of +1.18 on  $\text{C}_1$  and of -0.35 on oxygen, supported the belief that positive charge resided on  $\text{C}_1$ .



10

These two reports do not necessarily contradict each other because Olah and his coworkers<sup>4</sup> earlier showed that the chloride adducts were often complexes rather than ionic salts; however, moisture was not completely excluded, so the "weaker" chloride complexes could have been caused by hydrolysis of the Lewis acids. Boer's work certainly substantiated that the fluorides were ionic salts as Olah and his associates concluded.

NUCLEAR MAGNETIC RESONANCE STUDIES. One of the most powerful tools for investigating these adducts is nuclear magnetic resonance spectroscopy. Both proton (pmr) and  $\text{F}^{19}$  spectra were run on all of the adducts. Liquid  $\text{SO}_2$  was the most frequently used solvent, but  $\text{HF}$  was also employed.

As Olah and his coworkers<sup>4</sup> have emphasized, data on the crystalline compounds cannot be extended without further information on the structures of these adducts in solution. Solvation energy forces, as well as other interactions, replace the lattice energy forces of the solid compounds, and these effects could be important.

Many of the acyl fluorides exhibited  $\text{H}^1\text{-F}^{19}$  coupling of varying magnitude, and as expected none of the adducts showed any of this coupling; however, this evidence could not be considered a conclusive demonstration of ionic dissociation because fast exchange in a highly polarized donor-acceptor complex could also result in the absence of detectable coupling.<sup>4</sup>

In the spectra of primary and secondary adducts the absorptions of two species were present.<sup>4-6</sup> An example was acetyl fluoride whose  $\text{SbF}_5$ -adduct exhibited two singlets 4.08 (I) and 2.94 (I') ppm downfield from TMS.<sup>4</sup> The deshielding of the methyl signal indicated positive charge on either the carbon or oxygen atom. Species I was assumed to be the ionic salt and I' was believed to be the donor-acceptor complex. Later studies showed that the signal of I' disappeared when extreme steps were taken to exclude moisture from the sample.<sup>7,9</sup> When minute amounts of water were added to the samples the absorption attributed to I' appeared with concurrent loss of the other signal<sup>9</sup>, thus substantiating the conclusions made from the infrared data





discussed above.

With an empirical linear relationship<sup>14,15</sup> for the chemical shift ( $\delta_{\text{CH}_3}$  in ppm) of a methyl group adjacent to a moiety having a Huggins' electronegativity ( $\epsilon$ ) it was found that  $\epsilon$  was 3.74 for the

$$\epsilon = (1.29 - 0.6 \delta_{\text{CH}_3}) \text{ in ev}$$

methyl oxocarbonium ion. By comparing this value with some typical ones ( $\epsilon_{\text{NO}_3} = 3.90$ ,  $\epsilon_{\text{CN}} = 2.49$ ) it was shown that the methyl oxocarbonium ion was electron withdrawing, thus indicating positive charge on the ion.<sup>4</sup>

To further substantiate that some positive charge resided on the carbon atom of acylium ions, Olah and his associates<sup>6</sup> studied the  $\text{C}^{13}$  nuclear magnetic resonance of  $\text{CH}_3\text{C}^{13}\text{O}^+\text{SbF}_6^-$ . The  $\text{C}^{13}$  absorption was shifted -30.9 ppm relative to that of  $\text{CF}_3\text{C}^{13}\text{O}_2\text{H}$  and -45.5 ppm relative to that of  $\text{CH}_3\text{C}^{13}\text{OF}$ , thus confirming that at least a partial positive charge was located on the carbon atom.

The downfield shifts of the proton absorptions, indicating deshielding due to a positive charge, of several primary and secondary acylium ions are summarized in Table 2.

The  $\text{F}^{19}$  spectra indicated that the  $\text{SbF}_6^-$  ion was present in all of the adducts studied.<sup>4-9</sup> In cold HF exchange was slow enough so that both the solvent and anion peaks could be observed. No evidence existed, however, to exclude an exchanging, highly polarized F-SbF<sub>5</sub> system.

At -80° the pmr spectrum of the pivalyl fluoride-antimony pentafluoride adduct contained three methyl signals at -3.95, -2.02 (I), and -1.45 (I') ppm from TMS.<sup>6</sup>

Table 2a: Proton Chemical Shifts (in ppm)<sup>b</sup> of Alkyl Fluorides and Their Antimony Pentafluoride Adducts.<sup>c</sup>

Compound	Acyl Fluoride <sup>d</sup>			Oxocarbonium Ion <sup>d</sup>		
	$\text{CH}_3$	$\text{CH}_2$	CH	$\text{CH}_3$	$\text{CH}_2$	CH
$\text{CH}_3\text{COF}$	2.25d			4.08		
$\text{CH}_3\text{CH}_2\text{COF}$	1.2 q	2.4 t		2.1 q	4.5 t	
$(\text{CH}_3)_2\text{CHCOF}$	1.4 d		2.8 m	1.7ld		4.33sp
$(\text{CH}_3)_3\text{C-COF}$	1.27			2.02		

<sup>a</sup>From Ref. 4,6. <sup>b</sup>Relative to internal TMS. <sup>c</sup>In  $\text{SO}_2$  solution.

<sup>d</sup>d, doublet; t, triplet; q, quartet; sp, septuplet; m, multiplet.

The species causing the lowfield peak could not have been the oxocarbonium ion because the methyl groups of other secondary and tertiary acylium ions exhibited shifts of only -0.5 ppm from their parent acyl fluorides compared to this difference of -2.68 ppm. Even the absorption of the methyl oxocarbonium ion, in which the positive charge was only one carbon removed, had a shift of -1.83 ppm. Olah and his coworkers concluded that the *t*-butyl cation was causing the -3.95-ppm absorption, that the *t*-butyl oxocarbonium ion was producing the -2.02-ppm signal, and that a donor-acceptor complex was causing the -1.45-ppm peak. The pmr spectrum of *t*-butyl fluoride in  $\text{SbF}_5$  confirmed the assignment of the lowfield signal to the *t*-butyl cation. At room temperature the trimethylcarbonium ion disappeared, and a broadened peak attributed to polymer formation appeared.

The pmr spectra of the alkenyl oxocarbonium ions (9) indicated that they were predominantly ionic in  $\text{SO}_2$  from -40 to -60°.<sup>9</sup> Because the deshielding of the methyl protons  $\beta$  to the  $\text{C}=\text{O}^+$  was greater than that of the  $\alpha$ -methyl protons the authors assumed that the charge was delocalized by conjugation. Data on the cinnamoyl adduct indicated that the positive charge was also spread onto the phenyl ring (Table 3).

Olah and Comisarow<sup>7</sup> reported that all of the cycloalkyl adducts (8) were ionic in  $\text{SO}_2$  at -60°. The large deshielding of the ring protons led the authors to conclude that the positive charge resided primarily on the carbonyl carbon atom (Table 4). An attempt was made to decarbonylate the 1-adamantyl and 2-*exo*-norbornyl oxocarbonium ions to their respective, stable cations. Signals of the 1-adamantyl cation were



Table 3<sup>a</sup>: Chemical Shifts (in ppm)<sup>b</sup> of Alkenoyl Fluorides and Their Oxocarbonium Ions.<sup>c</sup>

Compound		Acyl Fluoride	Oxocarbonium Ion
CH <sub>2</sub> =C(CH <sub>3</sub> )COF	$\alpha$ -CH <sub>3</sub>	1.16	2.73
	$\beta$ - <u>cis</u>	6.13	8.45
	$\beta$ - <u>trans</u>	5.89	8.17
CH <sub>3</sub> CH=C(CH <sub>3</sub> )COF	$\alpha$ -CH <sub>3</sub>	1.55	2.62 (1.07) <sup>d</sup>
	$\beta$ - <u>cis</u>	6.88	9.33
	trans-CH <sub>3</sub>	1.61	2.82 (1.21) <sup>d</sup>
PhCH=CHCOF	$\alpha$	6.11	6.96
	$\beta$ - <u>cis</u>	7.57	9.40
	ring	7.27	7.90

<sup>a</sup>From Ref. 9. <sup>b</sup>From external TMS. <sup>c</sup>In SO<sub>2</sub> solution. <sup>d</sup>Magnitude of deshielding in ppm.

found after one day at room temperature, but none was detected for the norbornyl cation even though its parent acylium ion decomposed.

The nmr spectra of the SbF<sub>5</sub> adducts of the diacyl fluorides 9 led Olah and Comisarow<sup>8</sup> to decide that all those containing three or more methylene groups were dications in SO<sub>2</sub> from -30 to +60° (Table 4). The spectrum of the succinyl adduct supported the conclusions from the infrared data that it was a monooxocarbonium ion, monodonor-acceptor complex. The signal at -4.6 ppm was assigned to the methylene group adjacent to the ionic end, and the peak at -3.7 ppm was assigned to the methylene group next to the complexed end. The splitting of the highfield peak

Table 4<sup>a</sup>: Chemical Shifts (in ppm)<sup>b</sup> of Cycloalkylcarbonyl and Diacyl Fluorides and Their Oxocarbonium Ions.

Compound	Acyl Fluoride <sup>c</sup>				Oxocarbonium Ion <sup>c</sup>			
	H $\alpha$	H $\beta$	H $\gamma$	H $\delta$	H $\alpha$	H $\beta$	H $\gamma$	H $\delta$
Cyclopropyl	1.55m	1.1d			3.1b	3.1b		
Cyclobutyl	3.18m	2.2m	1.98m		4.95q	3.30m	2.6m	
Cyclohexyl	2.40b	1.60b	1.35b	1.17b	4.50m	2.60b	2.10b	1.80b
Succinyl	2.79				4.60t			
					3.73q			
Glutaryl	2.63	1.83			4.58t	3.34		
Terephthaloyl	7.59 <sup>d</sup>				8.07 <sup>d</sup>			

<sup>a</sup>From Ref. 7,8. <sup>b</sup>From external TMS. <sup>c</sup>d, doublet; t, triplet; q, quartet; m, multiplet; b, broad. <sup>d</sup>Main peak.

indicated that the fluorine atom was exchanging either very slowly or not at all in the complex. The F<sup>19</sup> spectrum contained a triplet 35.5 ppm downfield from external CFC1<sub>3</sub>, and the Sb-F signals appeared at +100 ppm; therefore the F<sup>19</sup> spectrum fully substantiated the conclusions based on the proton spectrum.

By interpreting the chemical shifts and splittings of H<sup>1</sup>, F<sup>19</sup>, and Cl<sup>35</sup> nmr spectra, Olah and his associates<sup>4-9</sup> have shown acyl fluoride-antimony pentafluoride adducts to be ionic salts in cold SO<sub>2</sub> solutions. That the results of the nmr investigations demonstrated that acylium ions exist in solution is important because these conclusions and those derived from the chemical reactions described below, both implicate acylium ions as intermediates in Friedel-Crafts reactions.

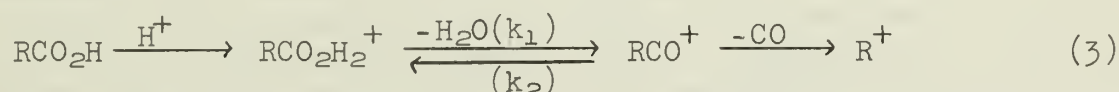




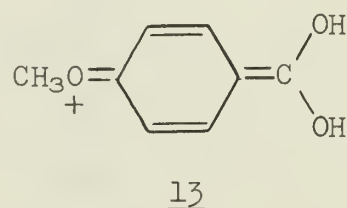
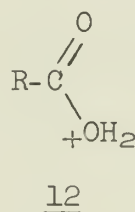
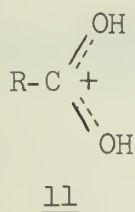
CHEMICAL REACTIVITY. All of the adducts except the tertiary oxocarbenium-hexafluoroantimonates were effective acylating agents in acylations of a variety of compounds.<sup>4-9</sup> Treating aromatic hydrocarbons with acylium salts produced aromatic ketones, O-acylation of alcohols yielded esters, S-acylation of mercaptans produced thioesters, and N-acylation of primary and secondary amines yielded amides. Both the *t*-butyl<sup>6</sup> and 1-adamantyl<sup>7</sup> oxocarbenium ions partially decarbonylated during their reactions to produce varying amounts of acylated and alkylated products. All of these reactions can be run under mild conditions (nitromethane as solvent), thus avoiding the sometimes harsh conditions of Friedel-Crafts acylations. That these acylium ions almost quantitatively produced acylated products certainly implicates their intermediacy in similar Friedel-Crafts reactions.

#### PROTONATED CARBOXYLIC ACIDS AND THEIR DEHYDRATION TO ACyliUM IONS

Cryoscopic<sup>16</sup> and spectroscopic<sup>17</sup> studies have shown that protonated carboxylic acids lose water to form acylium ions in strong acids. In some instances these oxocarbenium ions lose carbon monoxide to form alkyl carbonium ions<sup>18</sup> (eqn 3). Spectroscopic studies have elucidated the site of hydrogen attack and the stereochemistry of these protonated carboxylic acids.

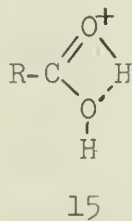
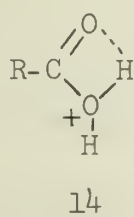


SITE OF PROTONATION. It was known that the carboxyl group was protonated in acidic media, but which of the oxygen atoms the hydrogen attacked was not known. Because of its resonance stabilization species 11 was preferred to 12.<sup>19</sup>



Stewart and Yates<sup>20</sup> used the possibility of charge delocalization to distinguish between 11 and 12 by studying the substituent effects on the basicities of twenty-two *meta*- and *para*-substituted benzoic acids. They reasoned that if species 11 were present direct resonance interaction like that in 13 could occur. A linear correlation was found when the basicities were plotted against the corresponding pK<sub>a</sub> values of the *meta*-substituted acids. A correlation with the Taft<sup>21</sup> σ<sub>+</sub> values was found for resonance interacting *para* groups. Also found was a good correlation between the basicities of the benzoic acids and those of the corresponding acetophenones which were known to protonate on the carbonyl oxygen.<sup>22</sup> From these results it was concluded that protonation of the carboxyl group was indeed occurring on the carbonyl oxygen atom.

Birchall and Gillespie<sup>23</sup> investigated the pmr spectra of carboxylic acids in SbF<sub>5</sub>-HSO<sub>3</sub>F solutions to determine the site of protonation. The pmr spectrum of benzoic acid contained a new peak (2 protons) similar to those found for protonated ketones. The authors could not distinguish between species 11 and 12 (R=Ph) with this data, since they could not rule out free rotation about the C-OH<sub>2</sub><sup>+</sup> bond in 12.



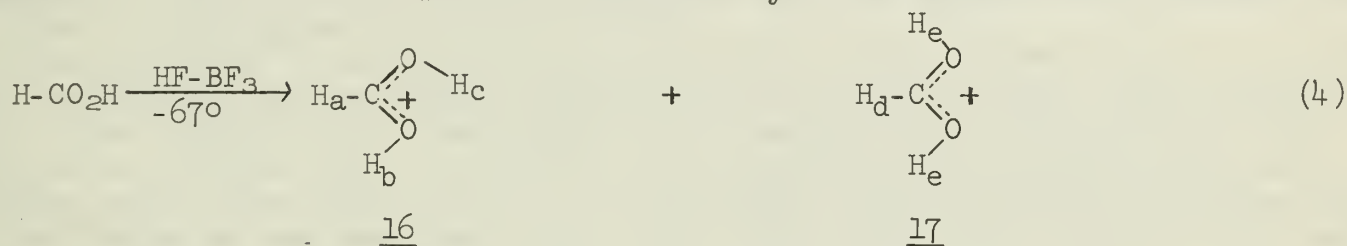
Acetic and propionic acids both exhibited two new peaks (1 proton each) at low field in SbF<sub>5</sub>-HSO<sub>3</sub>F. Birchall and Gillespie proposed that either 14 or 15 accounted for the observed spectra, assuming that hydrogen bonding would make the protons nonequivalent by preventing rotation about the C-OH<sub>2</sub><sup>+</sup> bond. Neither the new, lowfield signal nor the methylene peak of protonated ethyl acetate was split in the nmr spectrum, and it was



therefore decided that protonation of the ester had occurred on the carbonyl oxygen atom. This conclusion has been substantiated by Olah and O'Brien<sup>24</sup> who found coupling between the OH<sup>+</sup> proton and the methylene group of protonated ethers. By analogy Birchall and Gillespie concluded that species 11 and 15 had been produced.

Maciel and Traficante<sup>25</sup> detected one new species in the natural-abundance, C<sup>13</sup> nmr spectra of both protonated acetic and benzoic acids. The respective downfield shifts were 23 and 16 ppm from the parent acids. These values were compared with the respective 39 and 23 ppm downfield shifts observed when acetone and acetophenone were protonated. The substituted C<sup>13</sup> of protonated phenol, which was used as a model for hydroxyl oxygen protonation because of its sp<sup>2</sup>-hybridized C<sup>13</sup>, exhibited a shift of only 4 ppm, a much smaller effect also found in the C<sup>13</sup> spectra of protonated aliphatic ethers.<sup>26</sup> The authors therefore concluded that hydrogen had attacked the carbonyl oxygen of the carboxyl group. Olah and White<sup>27</sup> found similar downfield shifts in the C<sup>13</sup> nmr spectra of protonated acetic and benzoic acids in SbF<sub>5</sub>-HSO<sub>3</sub>F-SO<sub>2</sub> solutions. They noted that the deshielding must be due to some positive charge on the carbon since no hybridization changes occurred.

STEREOCHEMISTRY. In strong acid solutions of carboxylic acids at low temperatures proton exchange is slow enough to permit detection of both the solvent and the different hydrogens on the carboxyl oxygen atoms. The protonation of formic acid in HF-BF<sub>3</sub> at -67° was reported by Hogeveen and his coworkers<sup>28</sup> who found that two species (16 and 17) were present (eqn. 4). The assignments were based on coupling constants (J<sub>ac</sub> = 13.9, J<sub>ab</sub> = 3.2, J<sub>de</sub> = 2.4 cps), intensities, and double-resonance experiments. These results were substantiated by Olah and White<sup>29</sup> who studied formic



acid in SbF<sub>5</sub>-HSO<sub>3</sub>F-SO<sub>2</sub> at -60°. The two species were thought to be of about equal energy since a statistical distribution of 2:1 was found for 16:17. In a more recent report the above assignments were substantiated by J<sub>C<sup>13</sup>-OH</sub> data from HC<sup>13</sup>O<sub>2</sub>H<sub>2</sub><sup>+</sup>.<sup>27</sup>

Because no coupling involving the oxygen protons occurred in protonated acetic acid and its higher homologs, their nmr assignments have been based on those of formic acid.<sup>29</sup> Only one species like 16 with two, nonequivalent lowfield protons was observed for these higher homologs; however, two reports<sup>29,30</sup> of a second isomer of protonated acetic acid analogous to 17 have recently been made. Illustrative nmr data of protonated carboxylic acids are summarized in Table 5.

Table 5<sup>a</sup>: Chemical Shifts (in ppm)<sup>b</sup> and Multiplicities<sup>c</sup> of Protonated Carboxylic Acids.

Acid	OH	CH <sub>3</sub>	CH <sub>2</sub>	Alkenyl Protons
CH <sub>3</sub> CO <sub>2</sub> H <sub>2</sub> <sup>+</sup>	13.03 12.33	3.18		
	12.86	3.27		
CH <sub>3</sub> CH <sub>2</sub> CO <sub>2</sub> H <sub>2</sub> <sup>+</sup>	12.73 12.43	1.95t	3.67q	
CH <sub>2</sub> =CHCO <sub>2</sub> H <sub>2</sub> <sup>+</sup>	12.06(b) <sup>d</sup> 12.53(a) <sup>d</sup>			6.60-7.06(α) 7.25-7.88(β-cis and β-trans)

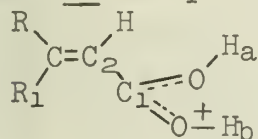
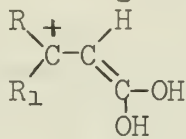
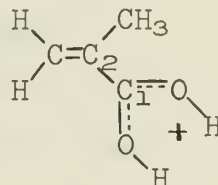
<sup>a</sup>From Ref. 29,31. <sup>b</sup>From external TMS. <sup>c</sup>t, triplet; q, quartet. <sup>d</sup>Refer to Species 18.







Olah and Calin<sup>31</sup> reported that  $\alpha, \beta$ -unsaturated acids were completely protonated in  $\text{SbF}_5\text{-HSO}_3\text{F-SO}_2$  at reduced temperatures (Table 5). One species with two nonequivalent lowfield protons was found when a hydrogen was in the  $\alpha$  position. The authors postulated that species 18 was present in all these acids if rotation around the  $\text{C}_1\text{-C}_2$  bond was facile compared to that around the  $\text{C}_1\text{-O}$  bonds. In crotonic acid the  $\beta$  proton was more deshielded than the  $\alpha$  proton, thus indicating conjugation with the double bond; however, because conjugation would have increased the barrier of rotation around the  $\text{C}_1\text{-C}_2$  bond, contributions from canonical forms like 19 were considered unimportant. Protonated  $\alpha$ -methylacrylic acid exhibited equivalent lowfield protons, and 20 was postulated, again assuming free rotation around the  $\text{C}_1\text{-C}_2$  bond.

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FORMATION OF ACYLIUM IONS. Protonated carboxylic acids can be dehydrated to acylium ions either by warming a solution of a stable, protonated carboxylic acid or by increasing the acidity of the medium (eqn 3).

Hogveen<sup>32</sup> studied the dehydration of protonated acetic acid in  $\text{HF-BF}_3$  as the temperature was raised from  $-80$  to  $-130^\circ$ . He determined that the first-order rate constant ( $k_1$ ) was  $4.1 \times 10^4 \text{ sec}^{-1}$  at  $-190^\circ$ , and that the second-order constant  $k_2$  for the reverse reaction was about  $10^3 \text{ l m}^{-1} \text{ s}^{-1}$ .

Olah and White<sup>29</sup> also found first-order kinetics for the dehydration of several alkyl carboxylic acids, and they reported that the relative rates ( $-240^\circ$ ) decreased in the order primary (1.46), secondary (1.23), and tertiary (0.56); on the same scale acetic acid was 1.00. These rates were determined in  $\text{SbF}_5\text{-HSO}_3\text{F-SO}_2$  as the solutions were warmed from  $-30$  to  $0^\circ$ . First-order kinetics were also reported for the dehydration of  $\alpha, \beta$ -unsaturated acids when their  $\text{SbF}_5\text{-HSO}_3\text{F}$ -solutions were warmed from  $0$  to  $+40^\circ$ .<sup>31</sup> At  $+1^\circ$  the relative rates were  $(\text{CH}_3)_2\text{C=CH-}$  (0.48),  $\text{H}_2\text{C=C(CH}_3\text{)-}$  (0.12), and  $\text{CH}_3\text{CH=CH-}$  (0.09). The chemical shifts found after dehydration were identical with those of the acylium ions obtained from the corresponding acyl fluorides.<sup>4-6,9</sup>

Deno and his associates<sup>33</sup> have traced the methyl oxocarbonium ion formation from protonated acetic acid as they increased the percentages of sulfuric acid and oleum ( $\text{SO}_3$ ) by following the change in the methyl absorption in the nmr. Between 13 and 17% oleum a sudden downfield shift of the methyl absorption indicated formation of the methyl oxocarbonium ion. No further change was detected as the  $\text{SO}_3$  concentration was increased to 65%.

Traficante and Maciel<sup>34</sup> have challenged these conclusions about the species in the oleum solutions. They followed the natural-abundance,  $\text{C}^{13}$  nmr shift of  $\text{CH}_3\text{C}^{13}\text{O}_2\text{H}$  as the sulfuric acid percentage was increased to 100% and agreed that the acetic acid was being protonated; however, they observed no signal until the oleum concentration reached 35% when an absorption 41 ppm higher than the protonated acid peak was observed. They believed that broadening of the signal could have caused its absence in the 10-20% range, but not at 25%  $\text{SO}_3$  where Deno and his associates reported that the acylium ion was formed. They also stated that this new peak was also about 50 ppm higher than the one Olah and his coworkers<sup>6</sup> reported for the  $\text{CH}_3\text{C}^{13}\text{O}^+$  ion; the structure of this new species was not postulated.

In a more recent study, however, Olah and White<sup>27</sup> have refuted the conclusions of Traficante and Maciel. They simultaneously monitored the  $\text{C}^{13}$  and proton magnetic resonance of 1- $\text{C}^{13}$  acetic acid as its  $\text{SbF}_5\text{-HSO}_3\text{F-SO}_2$  solution was warmed from  $-40$  to  $-10^\circ$ . An upfield shift of about 40 ppm occurred in the  $\text{C}^{13}$  nmr spectrum as the shifts in the proton magnetic resonance spectrum indicated acylium ion formation. These shifts were almost identical with those of Traficante and Maciel when both sets of data were related to  $\text{C}^{13}\text{S}_2$ . Olah and White believed that the "high-field" species of Traficante and Maciel actually was the oxocarbonium ion.



## CONCLUSIONS

The intermediacy of acylium ions in Friedel-Crafts acylations now appears to be firmly established. Infrared and nuclear magnetic resonance spectroscopy, and X-ray diffraction techniques have shown that these ions exist in both solution and crystalline salts. Oxocarbenium ions react with a variety of organic compounds to give products expected from Friedel-Crafts acylations. Oxocarbenium ions are also produced from protonated carboxylic acids whose site of protonation and stereochemistry have now been determined.

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# RECENT APPLICATIONS OF THE NUCLEAR OVERHAUSER EFFECT TO STRUCTURAL ORGANIC CHEMISTRY

Reported by Robert Farney

April 25, 1968

Analysis of high-resolution nuclear magnetic resonance (nmr) spectra is usually made on the basis of chemical shifts and coupling constants. Valuable information can also be obtained from observation of Nuclear Overhauser Effects (NOE's), a phenomenon dependent on the intramolecular spin relaxation pathways of nuclei. This subject has been reviewed;<sup>1,2</sup> proton-proton NOE's involving resonance intensity enhancements will be the subject of this seminar. The versatility of NOE's as a means of structural investigation will be emphasized.

## PHYSICAL BASIS OF THE NUCLEAR OVERHAUSER EFFECT

### Cross-Relaxation and Dynamic Polarization

If the spins of two nuclei are coupled in such a way that the relaxation of one spin affects the relaxation of the other, the nuclei are said to be cross-relaxed.<sup>3</sup> Thus a change in the distribution of nuclear spins among the energy levels of one nucleus causes a simultaneous change in the distribution of nuclear spins among the energy levels of the second nucleus. The nuclear spin population distributions of the two cross-relaxed nuclei are thus non-independent.

Thus, whenever cross-relaxation occurs, changes in the population of the spin states of spin A causes secondary changes in the populations for spin B. Dynamic polarization offers a method by which spin population differences between two levels may be increased many times above thermal equilibrium values. In a typical experiment, the transition of spin A is saturated by irradiation at the resonance line of A; changes in the population distribution of spin B are then observed at the resonance line of B.<sup>3</sup> Overhauser suggested<sup>4</sup> that dynamic polarization might be observed in the nuclear magnetic resonance of metals where the atomic nuclei and valence electrons form a strongly cross-relaxed system through coupling of electron and nuclear dipoles. This Overhauser effect was first confirmed by Carver and Slichter<sup>5</sup> by simultaneously observing the electron spin resonance and nuclear magnetic resonance of alkali metals. When the electron spin system was saturated by application of the appropriate microwave energy, the redistribution of nuclear spin states was verified by observation of signal enhancements in the nmr. Free radicals also show strong Overhauser effects through cross-relaxation of protons and the unshared electron.<sup>6-8</sup>

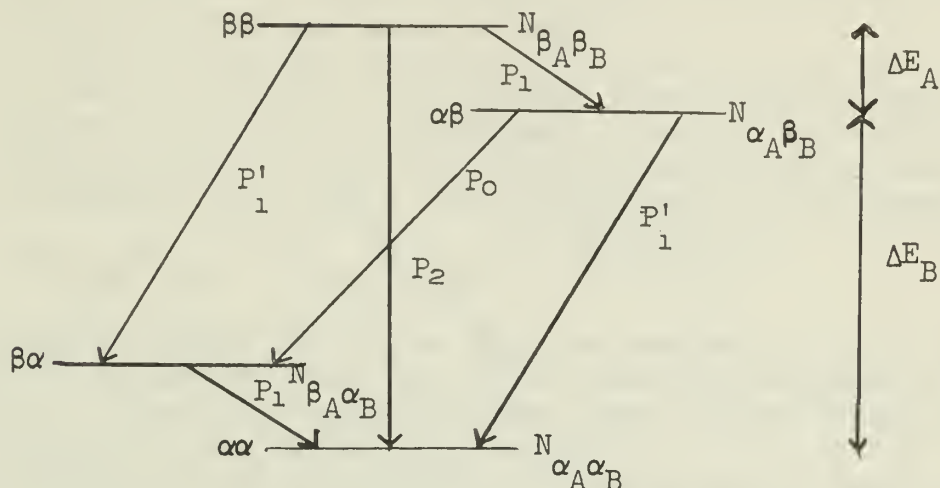
If two nuclei are strongly cross-relaxed through intramolecular direct dipole-dipole coupling, dynamic polarization of the nuclear spin states is also observable in the nmr. The Nuclear Overhauser Effect<sup>2,9,10</sup> results in intensity enhancements in nmr signals resulting from dynamic polarization effects induced by means of double resonance irradiation. Intermolecular<sup>11</sup> and intramolecular NOE's are possible, but the former can be minimized by dissolving the compound to be studied in a magnetically inert solvent or at least one containing no protons or fluorine nuclei, both of which possess strong magnetic dipoles.<sup>9</sup> Intramolecular NOE's are most pronounced in rigid molecules where direct dipole-dipole coupling of nuclei (as opposed to indirect dipole-dipole or spin-spin coupling) is the predominant means of nuclear spin relaxation.<sup>9</sup> Since the strength of the magnetic field of a nuclear magnetic dipole is inversely proportional to the cube of the distance from the dipole, observation of an NOE between two nuclei implies the nuclei involved are spatially close.<sup>9</sup> It should be noted that NOE's are not necessarily mutual; if the irradiation of nucleus A results in a signal enhancement in the resonance of nucleus B, saturation of nucleus B may not necessarily result in an enhancement of the signal of nucleus A.<sup>12</sup> This is because although nucleus A may relax predominately through the dipole of nucleus B, nucleus B may relax predominately through the dipoles of nuclei C or D, or through other relaxation mechanisms.

The Nuclear Overhauser Effect can be rationalized on the basis of the energy level scheme in Figure 1.<sup>1,2</sup> The diagram represents the four energy levels of two cross-relaxed nuclei contained in the same molecule where both nuclei have positive magnetogyric ratios and spins of  $\frac{1}{2}$ , i.e., protons. The same argument can be



extended to heteronuclear systems where the nuclei possess different spins and both positive and negative gyromagnetic ratios. The energy levels are denoted by

Figure 1.



horizontal lines; energy level differences are positive. The population of each energy level is indicated by  $N$  where  $\alpha$  and  $\beta$  refer to spin states in which the protons A and B have their magnetic moments aligned with and against the applied field, respectively.  $P_i$  are the transitional probabilities between energy levels.

The population differences between energy levels are proportional to the thermal equilibrium Boltzmann factor. Although the spin states will be in thermal equilibrium in the absence of an external field, the transitional probabilities in both directions between any levels, for example levels  $\alpha\alpha$  and  $\beta\alpha$ , may not be equal (equation 1). The nuclear spin population distribution ratio for levels  $\alpha\alpha$  and  $\beta\alpha$  is obtained (2) via the Boltzmann distribution. If the spin of proton B is saturated

$$N_{\alpha\alpha} \cdot P_{\alpha\alpha \rightarrow \beta\alpha} = N_{\beta\alpha} \cdot P_{\beta\alpha \rightarrow \alpha\alpha} \quad (1)$$

$$P_{\alpha\alpha \rightarrow \beta\alpha} / P_{\beta\alpha \rightarrow \alpha\alpha} = N_{\beta\alpha} / N_{\alpha\alpha} = e^{-\Delta E_A / KT} \quad (2)$$

by application of appropriate radiation, the two spin states of proton B become equally populated. Since protons A and B are cross-relaxed, the spin distribution of proton A also changes. Equations (3) and (4) describe the result. The ratio of

$$N_{\alpha\alpha} = N_{\alpha\beta} \quad (3)$$

$$N_{\beta\alpha} = N_{\beta\beta} \quad (4)$$

$$N_{\beta\alpha} / N_{\alpha\alpha} = N_{\beta\beta} / N_{\alpha\beta} = e^{-[\Delta E_A + \Delta E_B] / KT} \quad (5)$$

spin states  $N_{\beta\alpha} / N_{\alpha\alpha}$  is now as in (5). Since  $E_A$  and  $E_B$  are both positive, this

new population distribution favors an increase in the population (polarization) of the lower spin state in the A proton. The larger the polarization, the larger is the number of A protons available to undergo the energy absorbing process; thus an enhancement in the nmr signal of A is observed.

The intensity enhancement  $f$  obtained in the signal of proton A assuming complete saturation of the spin states of proton B is given by the general expression (6).<sup>3</sup>

$$f = \left( 1 + \left( \mu_B^I / \mu_A^I \right) \right) \quad (6)$$







Here  $\mu$  is the magnetic moment of the protons expressed in multiples of the nuclear magneton, and  $I$  is the spin of the protons expressed in multiples of  $h/2\pi$ . In practice, the intensity enhancement predicted by (6) is never attained due to incomplete saturation and the presence of non-direct dipole-dipole relaxation pathways between the nuclei involved.<sup>3</sup> Observed NOE intensity enhancements for  $^1\text{H}$ - $^1\text{H}$ ,  $^1\text{H}$ - $^{31}\text{P}$ , and  $^1\text{H}$ - $^{13}\text{C}$  coupled systems are given elsewhere.<sup>2,13</sup>

The population redistribution described by (5) occurs only if the predominant relaxation pathway of the two protons occurs through direct dipole-dipole coupling, i.e.  $P_2$ . If the relaxation mechanism is predominately scalar, i.e. involves spin-spin or indirect dipole-dipole coupling, the largest transitional probability will be  $P_0$ . Equation (7) describes the result. The polarization of the lower spin state

$$\frac{N_{\beta_A\alpha_B}}{N_{\alpha_A\alpha_B}} = \frac{N_{\beta_A\alpha_B}}{N_{\alpha_A\beta_B}} = e^{-(\Delta E_A - \Delta E_B)/KT} \quad (7)$$

for the A proton is thus reduced. If  $\Delta E_B \gg \Delta E_A$ , the population of the upper spin states for the A proton is greater than that of the lower and emission is observed in the resonance of A. Spin-spin coupling between A and B thus reduces the intensity enhancement (NOE) observed in the signal of proton A.

In summary, in order to observe an NOE (a) the predominant relaxation pathway for a nucleus must be through direct dipole-dipole coupling with a second nucleus; and (b) both nuclei must undergo a simultaneous spin flip in the relaxation process.<sup>3</sup> The intensity of the NOE signal enhancement observed (a) is diminished by spin coupling between the two nuclei involved; and (b) also depends upon the degree of saturation achieved in the nuclei irradiated.

#### PRACTICAL CONSIDERATIONS FOR THE OBSERVATION OF NUCLEAR OVERHAUSER EFFECTS

##### Instrumentation

An obvious requirement for the observation of NOE's is the ability to simultaneously observe the nmr signals of both nuclei involved. This presents no problem for  $^1\text{H}$ - $^1\text{H}$  systems and  $^1\text{H}$ - $^{13}\text{C}$  systems; the modifications of the spectrometer necessary to simultaneously observe  $^1\text{H}$ - $^{31}\text{P}$  resonance have recently been described.<sup>13</sup>

The instrumentation required to observe NOE's is essentially that of an ordinary double resonance experiment. In double resonance, frequency sweeps are preferred over field sweeps largely because of convenience. Also, in field sweep experiments where the saturating frequency is exactly centered on the resonance to be irradiated, there is a definite tendency for the signal intensity of the decoupled nuclei to be greater than predicted mathematically. The error becomes larger as the strength of  $H_2$  is reduced.<sup>14</sup> Two frequency sweep methods have been described,<sup>15</sup> both of which permit the use of very slow sweep rates.

Nuclear Overhauser Effects<sub>1</sub> are first observed when the saturating field strength  $H_2$  is on the order of  $(T_1 T_2 \gamma^2)^{-1/2}$ .<sup>15</sup> Here  $T_1$  and  $T_2$  are the spin-lattice and spin-spin relaxation times of the irradiated nucleus and  $\gamma$  is its magnetogyric ratio. This weak perturbation is desirable when energy levels and relaxation times are studied via NOE's. Complete saturation of a resonance (decoupling) occurs when (8) is obeyed.<sup>15</sup> Here  $J_{AB}$  is the spin-spin coupling constant between nuclei A and B

$$H_2 \gg J_{AB}(2\pi)/\gamma_A \quad (8)$$

and  $\gamma$  is the magnetogyric ratio of the nucleus being saturated. (If an NOE is to be observed between any two nuclei A and B, however,  $J_{AB}$  must be small.) Nuclear Overhauser Effects are usually observed with saturating rather than perturbing  $H_2$  fields, but this introduces the risk that a peak sharpening due to removal of unresolved coupling may be mistaken for an intensity increase. When decoupling occurs, the band width at half-height is reduced but the signal area remains unchanged; when an NOE is observed, the band width at half-height remains unchanged but the signal area changes through an increase in signal height.<sup>16</sup> A pulsing method ideally suited to observation of NOE's has recently been described which avoids the complications of the saturation technique.<sup>17</sup>

In observing an NOE, great care must be taken to avoid saturating the resonance of the nucleus whose intensity is being observed. The observing field  $H_1$  must be kept as low as is consistent with a reasonable signal to noise ratio.<sup>14,18</sup> Too low



a  $H_1$  sweep rate may also produce saturation in the nucleus whose signal is being measured.<sup>15,18</sup>

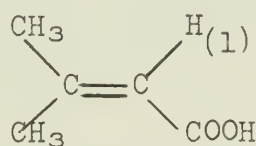
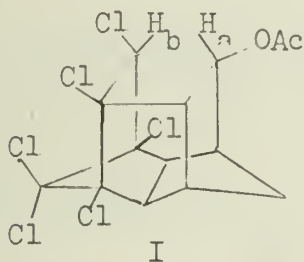
### Sample Preparation

Because the observation of an NOE is dependent upon the presence of a pre-dominant intramolecular dipole-dipole coupling mechanism, any other relaxation mechanisms between the nuclei involved diminish the observed intensity enhancement. Therefore paramagnetic impurities, such as oxygen, must be thoroughly removed prior to resonance studies.<sup>9</sup> The solvent should not contain nuclei that contribute to intermolecular dipolar relaxation.<sup>9</sup> Thus in theory solvents containing proton and fluorine nuclei should be avoided; commonly used solvents are  $D_2O$ ,<sup>9</sup> benzene- $d_6$ ,<sup>9</sup> deuteriochloroform,<sup>16,19,22</sup> and DMSO- $d_6$ .<sup>19</sup> In practice, however, strong NOE's are often observed despite the presence of fluorinated solvents.<sup>20,21</sup>

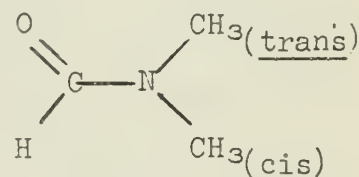
## RECENT APPLICATIONS OF NOE's TO PROBLEMS IN ORGANIC CHEMISTRY

### Conformationally Rigid Molecules

The half-cage acetate I showed a particularly strong NOE involving protons  $H_a$  and  $H_b$ . The protons appeared as equal intensity bands at  $\tau$  4.2 (width 3.6 Hz) and  $\tau$  4.52 (width 1.0 Hz), respectively. The value of  $J_{AB}$  was less than 1.0 Hz. When  $H_a$  was irradiated, the intensity of  $H_b$  increased by 45%. A similar enhancement in the intensity of  $H_a$  occurred upon irradiation of  $H_b$ . The dipolar interaction of  $H_a$  and  $H_b$  was so strong that the NOE could be observed even when oxygen was not removed from the sample. These signal enhancements were not due to the removal of any unresolved coupling since in both cases the line width of the non-irradiated band did not change upon enhancement. The  $H_a$ - $H_b$  internuclear distance has been estimated to be 0.9 Å.<sup>23</sup>



II



III

### Assignment of Spectral Bands via NOE

Nuclear Overhauser Effects are often a valuable tool in the assignments of bands in the nmr. The spectra of  $\beta,\beta$ -dimethylacrylic acid II, observed as a 9% solution in benzene- $d_6$ , showed the methyl groups as two doublets centered at  $\tau$  8.58 and  $\tau$  8.03;  $J_{Me-H(1)} = 1.3$  Hz for both doublets. Owing to virtually equal coupling to each of the methyl groups, the  $H(1)$  proton occurred as a septet at  $\tau$  4.34. Irradiation of either of the two methyl bands resulted in the proton septet being reduced to a 1:3:3:1 quartet. The integrated intensity of the quartet was higher when the high-field methyl group was irradiated (+17%) than when the low-field band was irradiated (-4%) relative to the proton area when no irradiation was performed. Thus the up-field methyl is cis to  $H(1)$ , in agreement with assignments based on chemical shifts.<sup>24</sup> Saturation of  $H(1)$  did not result in an intensity change for either of the methyl groups; thus  $H(1)$  contributes little to the relaxation of the methyl groups.<sup>9</sup> Observation of this NOE in II is unexpected since  $H(1)$  is ~~not~~ spin-spin coupled to both methyl groups.

Anet and Bourn<sup>9</sup> have carried out a similar experiment on N,N-dimethylformamide III. In the nmr of III, the methyl groups appear as two spikes located at  $\tau$  7.03 and  $\tau$  7.12.<sup>24</sup> In an 8% solution of III in  $D_2O$ , irradiation of the low field methyl results in an 18% increase in the integrated intensity of the formyl proton over that observed without irradiation. Irradiation of the high-field methyl results in a 2% decrease in the intensity of the formyl proton over that observed without irradiation. The low-field methyl ( $\tau$  7.03) is therefore cis to the formyl proton, in agreement with earlier assignments.<sup>25</sup>

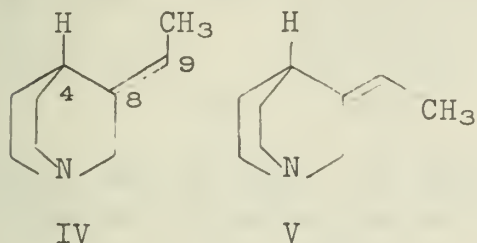


I



### Distinguishing Structural Isomers

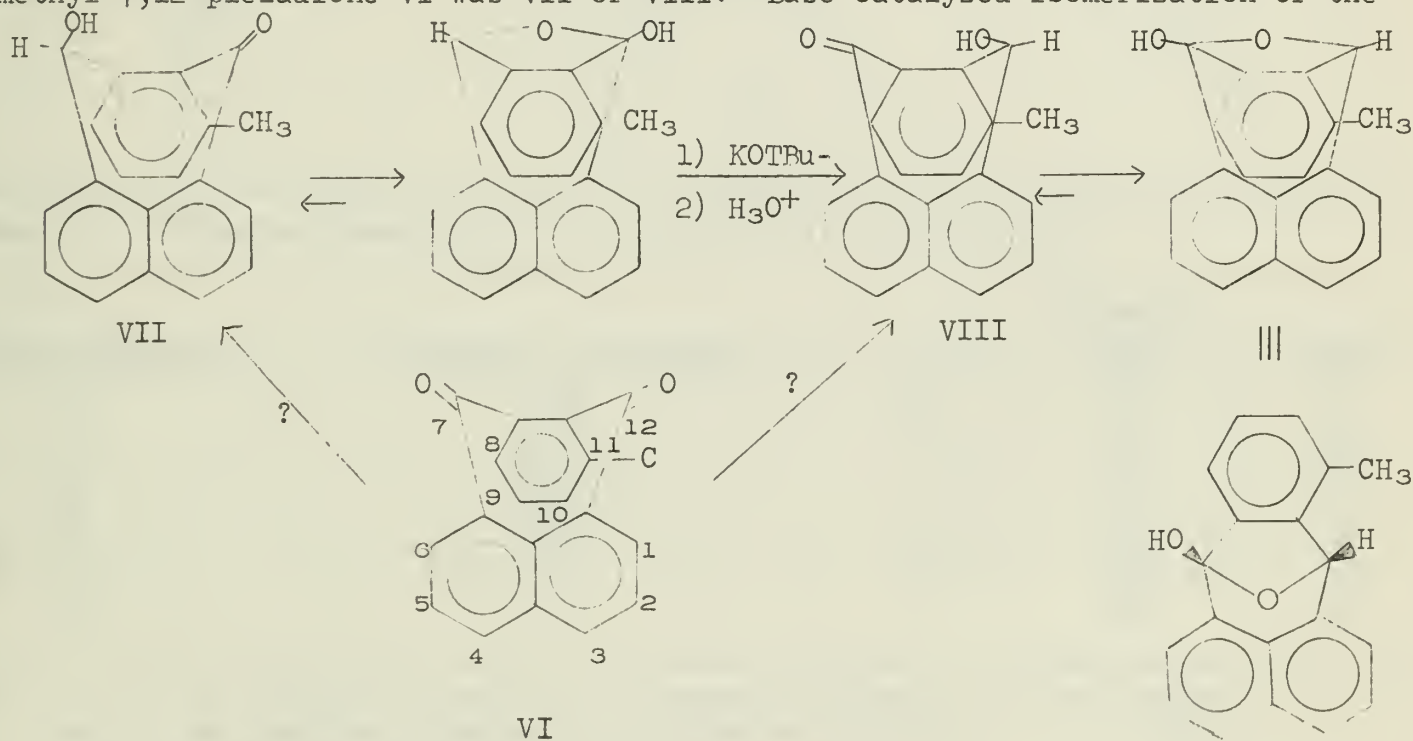
Nouls, Van Binst, and Martin<sup>20</sup> used an observed NOE to determine the major product of a Wittig reaction of triphenylethylphosphorane and 3-quinuclidone. In the 100 MHz nmr, the two isomers (IV and V, obtained as a 7/3 ratio) showed two quintuplets for the C-4 protons and two triplets for the C-9 methyl groups.



Irradiation of the lower field triplet resulted in a 31% enhancement of the low field quintuplet relative to the signal obtained without irradiation. The methyl group in IV is much closer to the C-4 proton than it is in V and thus must be responsible for the NOE. Since the methyl group irradiated constituted 70% of the total area of the methyl groups in the spectrum,

IV must be the isomer present as 70% of the reaction mixture. Thus the major product has the C-9 methyl substituent cis to the C4-C8 bond. Interestingly enough, this NOE was observed in a sample containing CF<sub>3</sub>COOH which might give rise to an intermolecular NOE. The authors argued, however, that since the measurements were carried out on a mixture of both isomers, their conclusions were not affected by the presence of the fluorine nuclei.

Lansbury, Colson and Saeva<sup>19</sup> have demonstrated the utility of the NOE as a structural tool when only small amounts of material are available. These workers desired to determine whether the product of a selective borohydride reduction of 8-methyl-7,12-pleiadione VI was VII or VIII. Base catalyzed isomerization of the

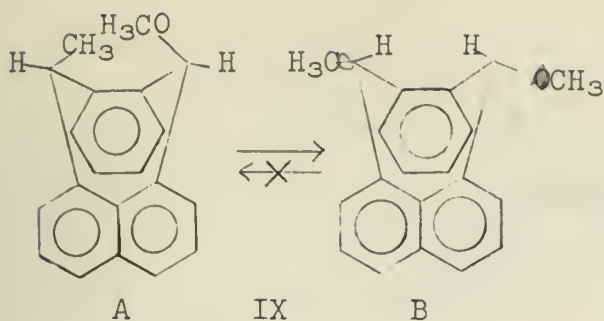


reduction product yielded a compound which, when the aryl methyl ( $\tau$  7.70) was irradiated, showed an intensity enhancement of 17% in the C-12 methine proton (relative to the ketol C-12 proton). This enhancement is possible only if the rearranged material was of structure VIII; thus the product of the reduction was assigned structure VII. This assignment was confirmed by similar irradiation of the aryl methyl of the unrearranged reaction product; no intensity increase was noted in the C-7 methine proton. The NOE was particularly valuable here in that both isomers were present in only milligram quantities and because both existed in hemiketal and ketol forms in solution at 35° C (hemiketal/ketol  $\approx$  3).

### Determination of Conformation and Stereochemistry

Lansbury et. al.<sup>19</sup> has shown how NOE's can be used to determine the preferred conformation of a molecule capable of inversion. cis-7-Methoxy-12-methyl-7,12-dihydro-pleiadene IX can exist in two conformations (A) and (B). When the C-12 proton





( $\tau$  5.04) was irradiated a 19% increase in the signal area was noted for the C-7 proton ( $\tau$  3.64). This NOE between transannular axial methine protons could occur only if B were the preferred conformer; that this is indeed the case is supported by other evidence.<sup>26</sup>

Woods *et. al.*<sup>21</sup> have used the NOE to determine stereochemistry in the ginkgolide series. Three of the ginkgolides studied were GC tetraacetate (X), isoGC tetraacetate (XI), and GA (XII). In Table I are listed the NOE's observed in these three compounds, given as the per cent increase in integrated intensity upon irradiation.

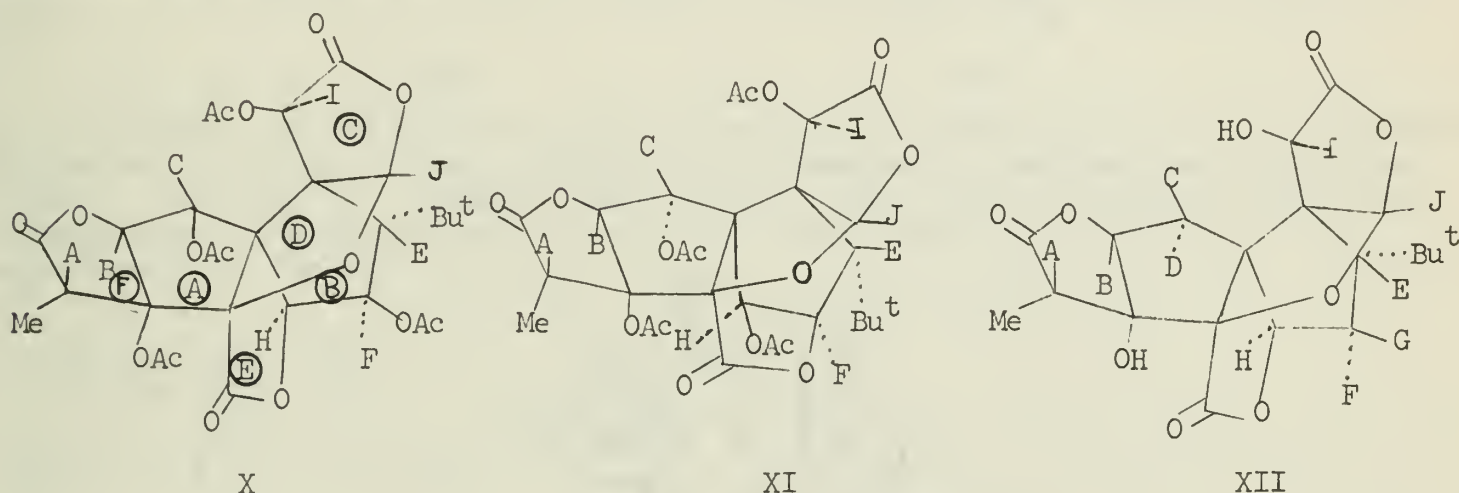


Table I. NOE Signal Enhancements<sup>a</sup> in Ginkgolides X, XI, and XII<sup>b</sup>.

Proton Observed	Proton(s) Irradiated	Compound		
		XI	X	XII
I	<u>t</u> -Bu	30	33	27
J	<u>t</u> -Bu	22	22	Nil
F	<u>t</u> -Bu	-- <sup>c</sup>	16	19
E	<u>t</u> -Bu	--	6	13
H	<u>t</u> -Bu	Nil	Nil	6
J	<u>E</u>	--	Nil	10
E	J	--	Nil	23

a. Given as the per cent increase in integrated intensity on irradiation.

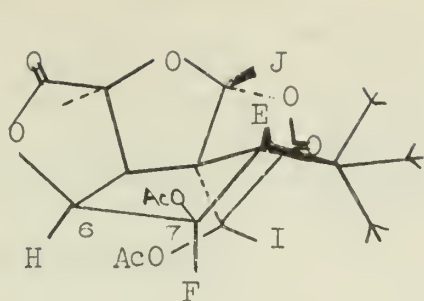
b. From 100 MHz spectra, obtained in trifluoroacetic acid.

c. Dash marks denote no intensity reported.

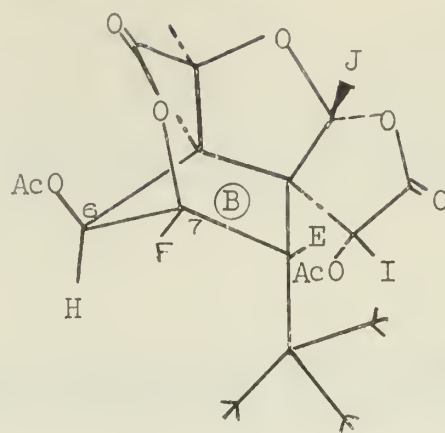
The observation of NOE's between the t-butyl group and protons I, J, F, and E in X required that the t-butyl group be close to all four protons. As partial structure XIII shows, this is the case if ring B is in the conformation shown with the t-butyl group in a quasi-equatorial position. When the conformation of ring B is changed to that observed in XIV where the t-butyl group occupies a quasi-axial position, proton J is no longer close to the t-butyl group and this NOE vanishes (see Table I). However, as is shown in partial structure XIV, proton H is now close to the t-butyl group giving rise to a new NOE, although of small intensity. The conformational change also brings protons J and E closer so that now a NOE is observed between them. These NOE's brought about by conformational changes in the B ring are consistent with the shift in the lactone ring from C-6 in X to C-7 in XI. A recent X-ray structure of GA confirms the stereochemical assignments obtained by NOE's.<sup>28</sup>





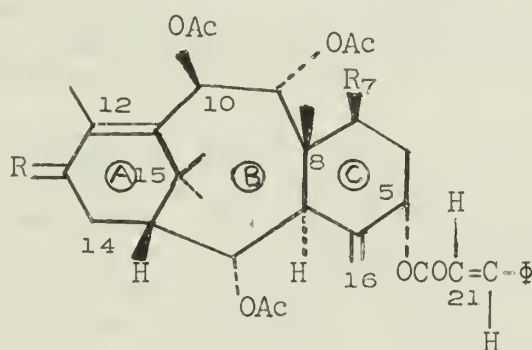
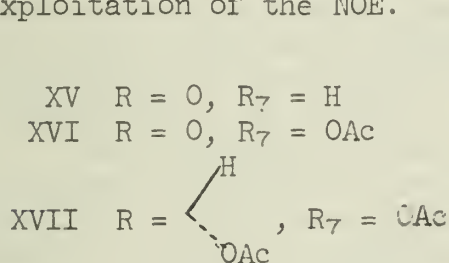


XIII

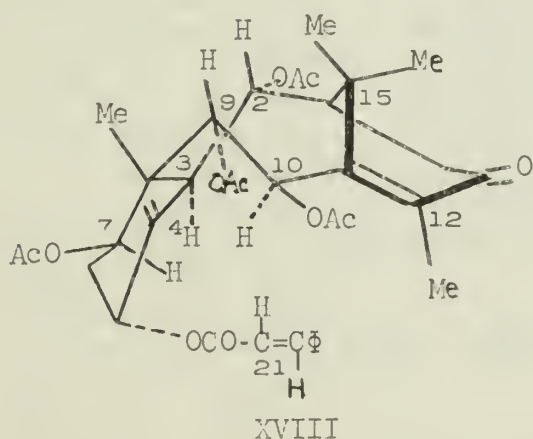


XIV

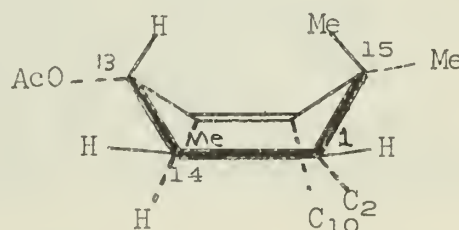
A dramatic use of NOE's as a stereochemical and conformational tool is illustrated by the work of Woods, Chiang, Nakadaira, and Nakanishi on taxinine and its derivatives.<sup>16</sup> Taxinine (XV) contains seven optical centers and Woods *et. al.* were able to demonstrate the stereochemistry of six of them, relative to that of C-1, by exploitation of the NOE.



Saturation of the 15 $\alpha$ -Methyl in XV gives rise to 10-20% intensity enhancements for protons 2 and 9; hence these protons must be  $\beta$  to the ring. Saturation of H-7 increases the signal area of H-10 by an unspecified amount; hence H-10 must be  $\alpha$ . Saturation of the C-12 methyl affects the C-21 and C-10 protons in a like manner. Thus the stereochemistry about four centers (C-2, C-5, C-9, and C-10) was defined relative to C-1. The only three dimensional model accounting for all NOE data is shown in XVIII. To obtain this conformation, ring juncture BC must be trans; thus the configurations at C-3 and C-8 are also defined.



XVIII



XIX

In taxinine TB, XVI, the stereochemistry about C-7 is defined by coupling constants between the 7 $\alpha$ -( $\tau$ 4.57, dd) and 6 $\beta$ -( $\tau$ 3.26, ddd) protons ( $J_{7\alpha,6\beta}$  = 11 Hz)



and by the NOE observed between the H-7 and H-10 protons.

In taxinine TJ, XVII, irradiation of 15 $\beta$ -methyl gives a 10-15% increase in the C-13 proton intensity; the C-13 proton must be assigned a  $\beta$  configuration. On the basis of this NOE the preferential conformation for the A ring must then be shown in the partial structure XIX. Taxinine TJ has nine asymmetric centers; observation of NOE's in taxinine and its derivatives have demonstrated the stereochemistry of eight centers relative to the ninth, that of C-1.

#### NOE INVOLVING HETERONUCLEI

##### <sup>13</sup>C-H

The observation of NOE's involving <sup>13</sup>C and protons has been suggested as a means of extending <sup>13</sup>C resonance to larger molecules and more dilute samples.<sup>18</sup>

##### <sup>31</sup>P-H

The observation of NOE's in <sup>31</sup>P-H systems has recently been described and intensity enhancements reported.<sup>13</sup>

#### SUMMARY

The NOE is a nuclear cross-relaxation phenomenon arising via direct dipole-dipole coupling and is observed through nuclear magnetic resonance. The intensity of signal enhancements depends upon internuclear separation and upon the degree that direct dipole coupling between the nuclei involved contributes to the spin relaxation of the nuclei.

No correlation of the intensity of NOE's with the internuclear distance has yet been made; clearly this relationship must be determined if the NOE is to assume its full utility as a structural tool. Some indication of the maximum distance at which a NOE may be observed can be gained by considering the ginkgolides discussed earlier. Ginkgolide GA shows an intensity enhancement of 22% for the J proton upon irradiation of the *t*-butyl band; the internuclear distance is estimated<sup>29</sup> as 2.82 $\pm$ 0.10 $\text{\AA}$ . When the conformation of the B ring is changed to that of isoGC tetraacetate, the internuclear distance<sup>29</sup> increases to 3.26 $\pm$ 0.10 $\text{\AA}$  and no NOE is observed between the *t*-butyl group and the J proton. In this instance, therefore, the maximum internuclear distance giving rise to a NOE between protons lies between 2.82 and 3.26  $\text{\AA}$ .

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30. The following papers concerning Nuclear Overhauser Effects have recently appeared in the literature: (a) K. Shirahata, T. Kato, M. C. Woods, Y. Kitahara, K. Ro, and T. Kurihara, Tetrahedron Lett., 16, 1993 (1968); (b) M. C. Woods, I. Miura, A. Ogiso, M. Kurabayshi, and H. Mishima, ibid., 2009; (c) T. Takahasni, H. Imamura, O. Honda, S. Ito, M. Kodama, and M. Sunagawa, ibid., 17, 2065 (1968).



# RECENT WORK ON SUBSTITUENT POLAR EFFECTS

Reported by Jimmy W. Worley

April 29, 1968

## INTRODUCTION

Substituents exert their influence on a reaction primarily by polar, resonance, and steric effects. The polar effect has been described as a through-space effect explainable by the classical laws of electrostatics, as a through-the-bonds effect due to a polarization of the intervening sigma bonds, or as a combination of both. The through-space interaction is called the "field effect," and the through-bonds interaction is called the "inductive effect." This seminar will consider work on field and inductive effects that has appeared since the last review<sup>1</sup> and also will discuss recent quantum mechanical calculations on substituent effects.

## THE FIELD EFFECT

Kirkwood and Westheimer<sup>2</sup> proposed that (a) the ratio of the statistically corrected first and second ionization constants of dicarboxylic acids and (b) the effect of a dipolar substituent X on the rate of ionization of a carboxylic acid could be predicted by equations (1)-a and (1)-b, respectively.

$$(1) \quad (a) \quad \log \frac{K_1}{4K_2} = \frac{e^2}{2.303 R k T D_E} \quad (b) \quad \log \frac{K_X}{K_H} = \frac{e \mu \cos \Theta}{2.303 R^2 k T D_E}$$

where  $e$  is the unit of charge,  $\mu$  is the substituent group moment,  $\Theta$  is the angle the substituent bond makes with the line from the center of the dipole to the ionizable proton,  $R$  is the distance from the ionizable proton to the (a) negative charge or (b) the center of the dipole,  $k$  is Boltzmann's constant,  $T$  is the absolute temperature, and  $D_E$  is the "effective dielectric constant." The evaluation of  $D_E$  imposes a major limitation on the Kirkwood-Westheimer equations. The molecule is considered mathematically as either a sphere or a prolate ellipsoid. Then equation (2) is applied, where  $D$  is the macroscopic dielectric constant of the solvent,  $D_i$  is the "internal dielectric constant" of the molecule, and is usually taken to be 2.0, the macroscopic dielectric constant of liquid paraffin hydrocarbons, and  $f_1$  and  $f_2$  are mathematical functions relating distances and angles of the charges and dipoles inside the spherical or ellipsoidal "molecular cavity." Tanford<sup>3</sup> later added an additional parameter, the depth of the charges and dipole inside the cavity. He found that this distance, the difference between the radius of the sphere and distance of the charge or dipole from the center of the sphere, has a significant bearing on the calculated result.

$$(2) \quad 1/D_E = f_1/D + f_2/D_i$$

## THE INDUCTIVE EFFECT

The inductive effect approach is due mainly to Branch and Calvin.<sup>4</sup> This theory proposes that the effect exerted by a substituent at an initial position is diminished by a constant factor per bond as the substituent is removed further from the reaction site. The effect is considered for all bonded paths from the substituent to the reaction site. This theory is expressed by equation (3), where  $\lambda$  is the substituent effect,  $s$  is the initial position of reference,  $n$  is the number of bonds from original substitution position  $s$ ,  $p$  is the number of paths, and  $\epsilon$  is the transmission coefficient. Most workers consider the fall-off factor per bond to be between 2 and 3, making  $\epsilon$  between 0.33 and 0.5. Bowden<sup>5</sup> proposed the  $\epsilon$  values of 0.48 for an  $sp^3$  carbon, 0.67 for an  $sp^2$  carbon, and 0.60 for an aryl carbon.

$$(3) \quad \lambda_{s \pm n} = \lambda_s \sum_p (\epsilon^s \pm n)_p$$

Much work has been interpreted in terms of either field or inductive effects, but most of it could actually be explained by either effect<sup>1,6</sup> since in the flexible chain systems studied, the values of  $R$ ,  $\Theta$ , and other parameters were doubtful, and in the rigid molecular systems investigated the field effect was constrained to





operate through the space containing the bonds that are important to the inductive effect. Therefore an appropriate choice of  $D_E$  or  $\epsilon$  could make the results consistent with either explanation. Nevertheless, some recent work comparing rigid systems permits at least a qualitative demonstration of the operation of the field effect.

# SUBSTITUENT EFFECTS IN THE BICYCLO[2.2.2]OCTANE AND RELATED SYSTEMS

Holtz and Stock<sup>7</sup> determined the dissociation constants for ten 4-substituted-bicyclo[2.2.2]octane-1-carboxylic acids (1) in 50% (wt) ethanol-water at 25°. The Kirkwood-Westheimer treatment using an ellipsoidal cavity gave very poor correlations of  $\log(K_X/K_H)$  with the observed values. The spherical model gave the correct trend, but the calculated values were only about half the observed ones. The Tanford modification gave satisfactory predictions of  $\Delta pK_A$  (less than ten per cent overestimation in most cases) except for the hydrogen and alkyl substituents, for which it underestimated the correct values by



1 X = H, Me, Et, CH<sub>2</sub>OH,  
OH, OMe, CO<sub>2</sub>Et, Cl,  
Br, NO<sub>2</sub>

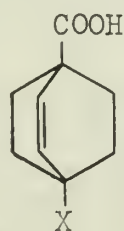
twenty per cent.

For the bromine substituent Holtz and Stock also made the calculation treating the carbon-bromine dipole as two point-charges instead of a point dipole and obtained a ten per cent better prediction.

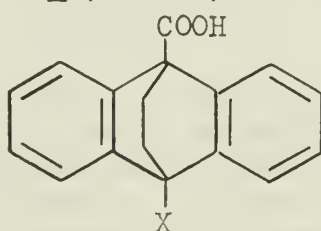
Wilcox and McIntyre<sup>8</sup> also reported results for some compounds 1, and they included some charged substituents in their study. They assumed the correctness of the method (Tanford's modification) and calculated apparent depths of the charges and dipoles inside the cavity for various substituents. These results were then used to predict changes in the cavity depth with changes in the nature of the charged substituents. They also determined the calculated dependence of  $\Delta pK_A$  on external dielectric constant, and therefore change in solvent. They found (a) that plots of theoretical  $\Delta pK_A$ 's against the reciprocal of the external dielectric constant are linear, as required by equations (1) and (2); (b) the lines for acids with charged substituents have much greater slopes than those with dipolar substituents; and (c) the ratio of the theoretical  $\Delta pK_A$ 's of all pairs of dipolar substituted acids are nearly constant over the normally studied range of D of 20 to 80, while the ratios of the  $\Delta pK_A$ 's of the charged acids to the dipolar acids change by a factor of two or more over this range. Thus solvent dependence is predicted to vary with substituent type by the Kirkwood-Westheimer relations.

These two reports demonstrate that a field effect model does predict trends in acidity, although an empirical fit of parameters in individual cases is necessary for reasonable quantitative agreement. One criticism that may be made of this work, however, is the use of the mixed solvent (50% ethanol-water), which was necessary due to solubility problems in the system. Unpredictable attractions of the various charges and dipoles for the two solvents might possibly invalidate the effective dielectric constant, derived on the basis of a uniform continuum of water and ethanol molecules.

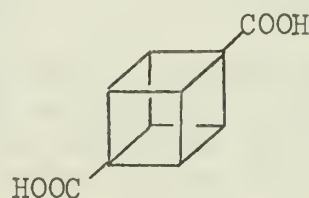
Additionally, no correlation of observed data with an inductive model was attempted, although Baker, Parish, and Stock<sup>9</sup> have reported further work in this system designed to distinguish between the two possibilities. They determined  $pK_A$  values of 4-substituted-bicyclo[2.2.2]octane-1-carboxylic acids (1), 4-substituted-bicyclo[2.2.2]octene-1-carboxylic acids (2), 4-substituted-dibenzobicyclo[2.2.2]octa-2,5-diene-1-carboxylic acids (3), and 1,4-cubanedicarboxylic acid (4). In all



2



3



4

of these compounds the portion of the molecule connecting the reaction site to the point of substitution is rigid, and the distance R is essentially the same.



However, they do differ in the number and kinds of bonds between substituent and reaction site. Therefore the inductive model predicts a difference in substituent effects among them, while the field effect model predicts no essential differences.

The  $\epsilon$  values suggested by Bowden<sup>5</sup> predict that  $\log(K_X/K_H)$  for the octene and dibenzo acids should be 1.3 and 1.4 times, respectively, that of the octane acids. Figures 1 and 2 show the observed values of the octene and dibenzo acids plotted against those of the octane acid, respectively.

Fig. 1

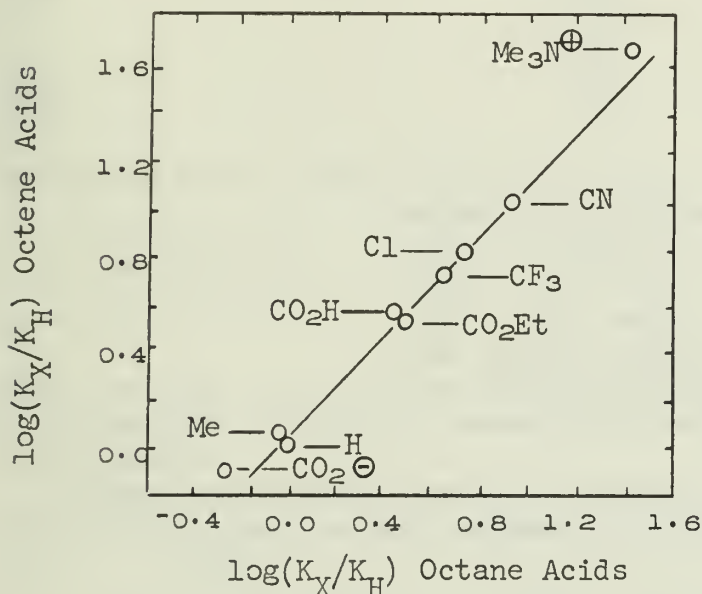
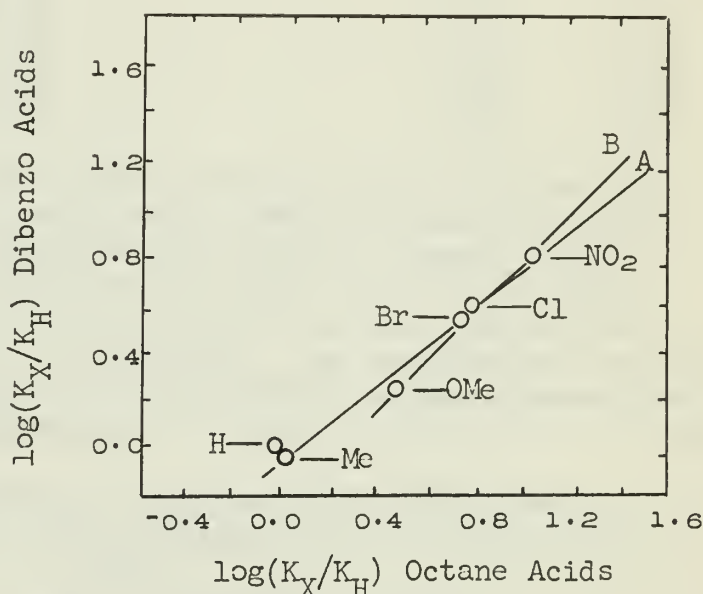


Fig. 2



The slope of the line in Fig. 1 suggests that substituent effects are propagated slightly more effectively (about 1.07-fold) through the octene structure. In Fig. 2 two least-squares lines have been constructed. Line A, which includes all the substituents studied, indicates that substituent effects are propagated less efficiently (about 0.75-fold) through the dibenzo structure. Line B, which excludes the hydrogen and alkyl substituents, has a slope of almost unity, indicating equal propagation through the octane and dibenzo structures. Hydrogen and alkyl groups often deviate from linear free energy relationships,<sup>1</sup> and therefore the authors preferred line B as a more meaningful estimate of the transmission efficiency.

The 1,4-diacids of compounds 1, 2, and 4 were examined to determine the influence of the number of paths available on the propagation efficiency. There are six 3-bond paths in cubane compared to three 3-bond paths in the bicyclic acids. Therefore the inductive model predicts that the statistically corrected ratio of the first and second dissociation constants,  $\log(K_1/4K_2)$ , should be twice as great for the cubane acid as for the bicyclic acids. The observed values and those calculated by the Tanford model are given in Table 1.

Table 1 Parameters and Calculated and Observed Values of  $\log(K_1/4K_2)$  for 1,4-Diacids

Acid	R (Å)	$D_E$	$\log(K_1/4K_2)$	
			Calculated	Observed
Octane	8.57	39.8	0.715	0.768
Octene	8.63	40.0	0.706	0.742
Cubane	8.67	40.1	0.701	0.798

The results in Table 1 show that the observed values are in extremely good agreement with a field effect model and incompatible with an inductive model.

In this work, the Tanford modification gave very poor calculated  $\Delta pK_A$  values when the reference was hydrogen; however, if some other reference was chosen, the calculated values were in good agreement with observed ones, as is shown in Table 2.

Wilcox and Leung<sup>6</sup> have compared the dissociation constants of some 4-substituted-bicyclo[2.2.2]octane-1-carboxylic acids (1) and 4-substituted-bicyclo[2.2.1]heptane-1-carboxylic acids (5). The number of paths in these two systems is the same, but







Table 2 Calculated and Experimental Log ( $K_X/K_{Cl}$ ) for Bicyclic Acids in 50% (wt) Ethanol-Water at 25°

Substituent	Octane Acids (1)		Octene Acids (2)	
	Calcd.	Exptl.	Calcd.	Exptl.
Cl	0.00	0.00	0.00	0.00
CN	0.05	0.19	0.08	0.23
CO <sub>2</sub> Et	-0.36	-0.27	-0.35	-0.28
CF <sub>3</sub>	-0.14	-0.12	-0.15	-0.07
Me	-0.58	-0.76	-0.57	-0.78
H	-0.53	-0.74	-0.53	-0.82
NMe <sub>3</sub> <sup>+</sup>	1.02	0.76	0.99	0.88
CO <sub>2</sub> <sup>-</sup>	-0.96	-0.96	-1.04	-1.00

one path is one carbon shorter for (2). Application of appropriate distances and angles to a Tanford cavity model gives a prediction of the ratio of  $\Delta pK_A$  for compounds 2 to  $\Delta pK_A$  for compounds 1 of 1.20. An inductive model predicts the ratio to be 1.33 to 1.67. This range includes all values of fall-off factors that various workers have proposed. The experimental results gave the ratio as 1.175 for water as solvent, 1.181 for 25% (v) methanol-water, and 1.172 for 50% (v) methanol-water, in close agreement with the calculation for a field effect model.

Holtz and Stock<sup>10</sup> have also reported rates of reaction of 4-substituted-bicyclo[2.2.2]octylmethyltosylates (6) with sodium thiophenolate, an S<sub>N</sub>2 reaction.



The plot of log ( $k_X/k_H$ ) for the reaction against log ( $K_X/K_H$ ) for the ionization of compounds 1 is linear, indicating that the rate of the displacement reaction also correlates with the prediction of a field effect model, and that a transition state similar to that in Fig. 3 could give the observed results.

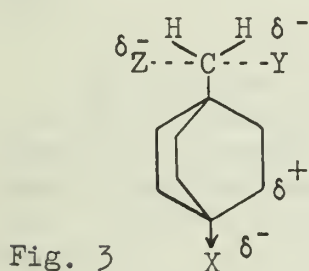
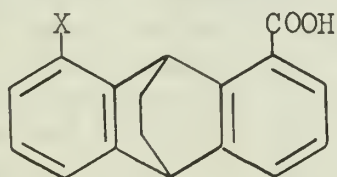


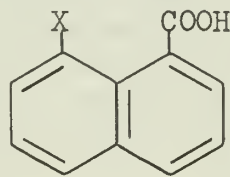
Fig. 3

Some recent work on "horseshoe" type compounds, in which the substituent is held in an atypical position close to the reaction site, gives the most convincing evidence for a field effect. Golden and Stock<sup>11</sup> have found reversed substituent effects in the ethano-bridged anthracenes (7). They found  $K_{Cl}$  and  $K_{COOMe}$  were less than  $K_H$ , a reversal of the effect normally exerted by these two substituents. This reversal is due to a disproportionally strong influence of the

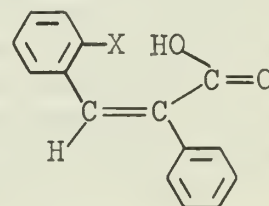
"negative" end of the dipolar substituent (C-X) which is held close to the reaction center. Bowden and Parker<sup>12</sup> have recently reported reversed dipolar substituent effects in the 8-substituted-1-naphthoic acids (8), and abnormal effects in the cis-ortho-substituted- $\alpha$ -phenylcinnamic acids (9).



7



8 X=H, Cl, Br, NO<sub>2</sub>, Me



9 X=H, Cl, Br, NO<sub>2</sub>

In summarizing the work on the bicyclo[2.2.2]octane and related systems, the major qualitative dominance of field effects over inductive effects has been clearly established, and, at least in these rigid systems, an empirical adjustment of parameters allows fairly satisfactory quantitative calculations of substituent effects to be made. The predictions fail for hydrogen and alkyl substituents, however.



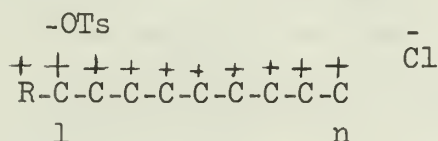
-OTs

$\begin{array}{cccccccccc} + & + & + & + & + & + & + & + & + \\ \text{R}-\text{C}-\text{C}-\text{C}-\text{C}-\text{C}-\text{C}-\text{C}-\text{C}-\text{C} \end{array}$

l    n

Cl<sup>-</sup>

Fig. 4



Therefore the substituent effect would be an electrostatic one but not with the charge and dipole in previously defined, localized positions. Furthermore, having some of the charge delocalized deep inside the molecular cavity would make interaction with the solvent less well defined than in the Kirkwood-Westheimer model.

## CORRELATION OF FLUORINE-19 CHEMICAL SHIFTS WITH SUBSTITUENT EFFECTS

In 1962, Dewar and Grisdale<sup>17</sup> reported an empirical method for incorporating both non-conjugative effects (polar effects) and conjugative effects into a single model for computation of Hammett-type sigma constants. The equation used for this procedure is shown in equation 4.

$$(4) \quad \sigma_{i,j} = F/r_{i,j} + M\rho_{i,j}$$

They proposed an  $r^{-1}$  dependence of the field effect instead of  $r^{-2}$ , and defined  $r$  as the distance between the two carbons to which the substituent and reaction center are attached. The argument for this was that the dipolar substituent would be solvated and that the dipole length was comparable to  $r$  in many cases, and therefore the reaction site would effectively "see" only the nearer end of the dipole, a monopole.

In equation (4),  $p_{ij}$ , the Hückel MO pi-electron coefficient, is either the charge density,  $q_{ij}$ , or atom-atom polarizability,  $\pi_{ij}$ , at AO site  $j$  induced by the substituent  $sp^2$  carbons introduced at site  $i$ . The F and M parameters are calculated from known values of  $r$ ,  $\sigma_m$ ,  $\sigma_p$ , and  $p_{ij}$  for substituted benzenes. Dewar and Grisdale applied the theory to the dissociation and esterification reactions of thirty-three substituted-1-naphthoic acids. The rates gave a reasonably linear correlation with the sigma constants calculated by equation (4) except for the 7-substituted acids.

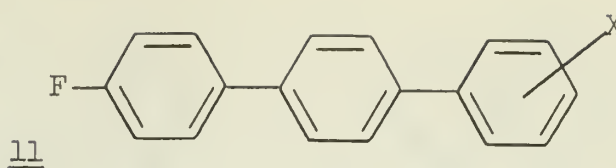
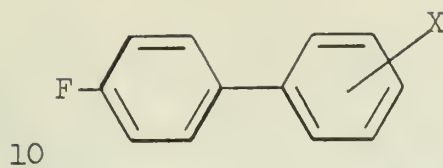
Wells and Adcock<sup>18</sup> applied Dewar and Grisdale's FM method to the dissociation and esterification of the 2-naphthoic acids and found good agreement of reactivity with the FM sigma constants, except for the 8-substituted acids. The anomalous results in the 1,7 and 2,8 acids were later attributed by Adcock and Dewar<sup>19</sup> to a dipolar effect as previously noted.

Dewar and Marchand<sup>20</sup> found that fluorine-19 "substituent chemical shifts," defined as the difference in chemical shifts of a substituted compound and of the compound with the substituent replaced by a hydrogen atom, correlated well with FM sigma constants. The compounds studied were 3'- and 4'-substituted-4-fluorobiphenyls (10) and 3"- and 4"-substituted-4-fluoroterphenyls (11). In the latter case the data were more consistent with an  $r^{-2}$  dependence.



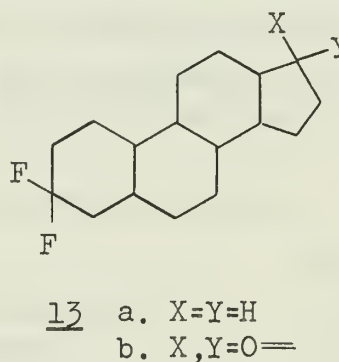
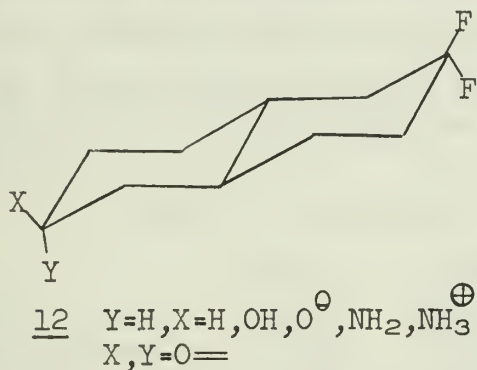






As noted, Adcock and Dewar recognized the dipolar influence of the substituent (i.e. the need for an angular dependence) and therefore the fact that the FM approach was an undue oversimplification. Bearing this in mind, and also substituting the SCF-MO method for calculating  $\pi_{ij}$ , they investigated fifty-five 1- and 2-fluoro-naphthalenes with substituents in most positions. They found that again the "substituent chemical shifts" correlated well with FM sigma constants if they included a  $\cos \theta$  term in the field effect parameter, where  $\theta$  is the angle between a line drawn through the carbon-fluorine bond and a line drawn from the midpoint of the carbon-fluorine bond to the carbon bearing the substituent. This is not the same angular dependence as in the Kirkwood-Westheimer equation. The KW angular dependence predicts smaller substituent effects for the 1,7-compounds than for the 2,8-compounds, as was found in the naphthoic acids, but opposite to that found in the fluoronaphthalenes. Adcock and Dewar's angular dependence was attributed to an anisotropic response of fluorine to an applied field. The argument was that the change in chemical shift of fluorine is presumably due to a polarization of the electrons forming the carbon-fluorine bond, and that this should depend on the field along the axis of the bond rather than the field perpendicular to it.

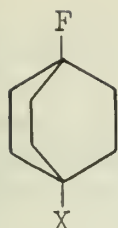
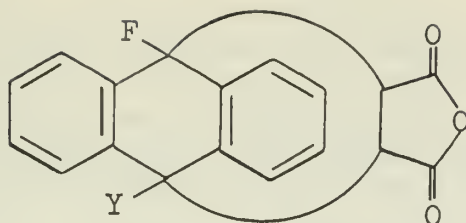
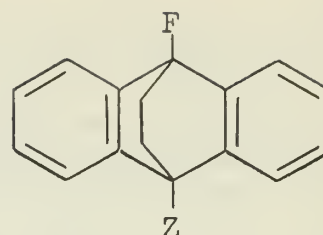
In a recent communication Dewar and Squires<sup>21</sup> reported F-19 chemical shifts in some saturated systems--substituted trans-decalins (12) and substituted androstanes (13).



The results found for these two systems were somewhat unexpected. First, equatorial fluorines in the 2-position of decalin were deshielded by +I substituents in the 6-position, while the effect on an axial fluorine substituent was small. If the substituents acted by electrostatic polarization of the carbon-fluorine bond, one would expect a greater effect on equatorial than on axial fluorines, but the resulting chemical shift should be in the opposite direction. They also found no detectable differences in F-19 chemical shifts for compounds 13-a and 13-b, contrary to the expectations based on a field effect model.

They further found there was no detectable difference in going from -OH to -O<sup>-</sup> or from -NH<sub>2</sub> to -NH<sub>3</sub><sup>+</sup> in the decalins, again indicating the effects were not due to simple electrostatic polarization of the carbon-fluorine bond. Dewar and Squires surmised that when a fluorine atom is attached to a conjugated system, the p-electrons of the strongly electronegative fluorine will not be delocalized into the pi-system and therefore any polarization of the carbon-fluorine pi-bond will involve orbitals that are mainly concentrated on fluorine. They also concluded that the major determinants of F-19 chemical shifts in these alicyclic systems were strictly stereochemical in nature, being due to conformational distortion of the carbon skeleton. Eliel and Martin<sup>22</sup> have investigated conformational analysis of fluorocyclohexanes by F-19 nmr and found that the position of the fluorine signal is affected by 3- and 4-t-butyl groups. Further, Anderson and Stock<sup>23</sup> have determined F-19 substituent chemical shifts for compounds 14, 15, and 16, and have found that the data indicated modest influence of polar effects (whether inductive or field) on the fluorine chemical shifts of these compounds. They suggest the differences are also steric in origin.



14 X=H, COOEt, F15 Y=Br, CO<sub>2</sub>Me, CN16 Z=OCOMe, Cl, Br, CO<sub>2</sub>Me, CN, NHCOMe, NO<sub>2</sub>

In conclusion, it is seen that Dewar and Grisdale's FM method can give reasonable trends of reactivities in aromatic systems but only by empirical variations of the parameters for each system. In light of their recent evidence, it is not clear why the method should give a satisfactory correlation with fluorine-19 chemical shifts in these systems.

#### QUANTUM MECHANICAL CALCULATIONS OF POLAR EFFECTS

Some very interesting results have recently been reported by several workers, attempting to describe polar effects with the aid of molecular orbital calculations. Pople and Gordon<sup>24</sup> used the approximately self-consistent m.o. theory CNDO (complete neglect of differential overlap) to calculate charge distributions and electronic dipole moments for a series of simple organic molecules (sixty-one compounds, including hydrocarbons and fluorine-, oxygen-, and nitrogen-containing compounds of up to five carbons). They used standard bond lengths, bond angles, and dihedral angles for the calculations. The calculations reproduced all major series trends, as



The quantitative agreement between calculated and experimental dipole moments was very good, with few molecules being seriously in error. See Table 3 for some examples.

Table 3 Calculated and Observed Dipole Moments (Debye)

	<u>Cal</u>	<u>Obs</u>		<u>Cal</u>	<u>Obs</u>
Propane	0.00	0.083	Formaldehyde	1.98	2.339
2-Methylpropene	0.65	0.503	Acetone	2.90	2.90
Fluoroform	1.66	1.645	Phenol	1.73	1.55
Fluoroethylene	1.51	1.427	Hydrogen Cyanide	2.48	2.986
n-Propylfluoride	1.85	2.05	Formamide	3.79	3.71

The most significant result of this work, however, was a theoretical prediction of alternating inductive effects in both pi- and sigma-bonded systems. Typical results are shown for some fluorine compounds in Fig. 5; the numbers refer to calculated atomic charge densities ( $10^{-3}$  electron unit) and fractions have been rounded to nearest whole numbers.

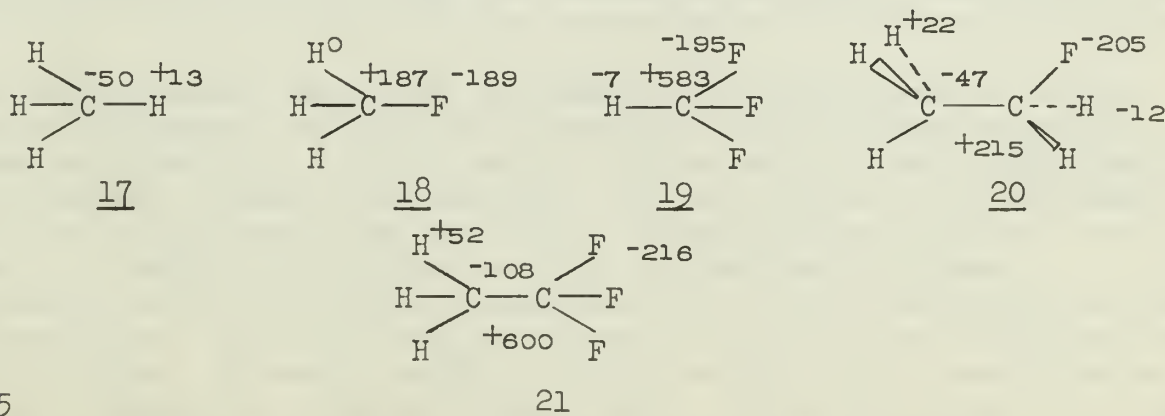


Fig. 5

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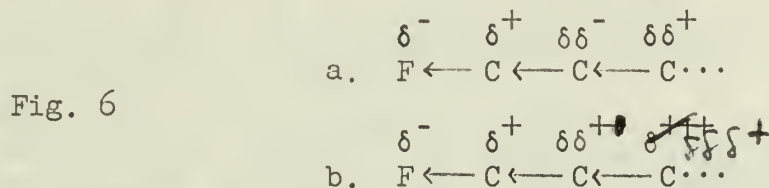
In methyl fluoride (18) the main effect is a transfer of electrons from carbon to the more electronegative fluorine, but a secondary effect is that the hydrogens





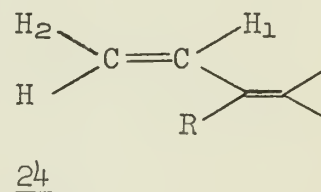
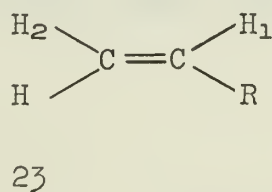
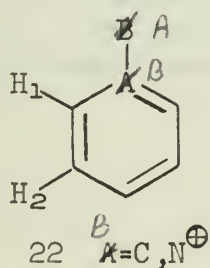


are slightly more negative than in methane (17). This negative character of atoms separated by two sigma bonds from the substituting fluorine is also apparent in fluoroform (19) and becomes more evident in ethyl fluoride (20) and 1,1,1-trifluoroethane (21). These results were interpreted by Pople and Gordon as implying an alternating inductive effect (Fig. 6-a) rather than the ordinary inductive effect that predicts a monotonic decrease of effects as one proceeds down the chain (Fig. 6-b).



A physical interpretation of this phenomenon is that fluorine acts as a strong sigma-electron attractor, removing electrons from the carbon to which it is attached, and also as a weak pi-electron donor in which these electrons go to the beta-position. This interpretation is supported by the calculations when the electron distribution of  $CH_3F$  is broken down into sigma- and pi-contributions. The pi-bond order on fluorine is slightly less than 2.0 (1.979), implying the back-donation. The authors found similar alternating effects for hydrocarbons, for which hyperconjugation is proposed, and for nitrogen and oxygen compounds. It would be interesting to see the calculations for longer carbon chains to see how rapidly the calculated effect dies and also for one of the "horseshoe" compounds to see if the observed dipole moment is reproduced.

Castellano and Kostelnik<sup>25</sup> have observed an alternating effect of substituents on the vicinal proton-proton coupling constants of two series of compounds. For a constant substituent B in substituted benzenes and pyridines (22), they found  $J_{12}$  directly proportional to the electronegativity of atom A, but for a constant atom A,  $J_{12}$  was inversely proportional to the electronegativity of atom B. They observed a similar alternating dependence of  $J_{12}$  for some monosubstituted ethylenes (23) and 2-substituted-1,3-butadienes (24).



$R = H, t-Bu, Me, I, Br, Cl, F, OMe$

## CONCLUSION

The nature of the substituent polar effect is better understood now than it was a few years ago. The study of substituent effects on the rates of dissociation and esterification of acids having rigid and horseshoe structures has yielded results consistent with a field effect model and inconsistent with a classical inductive model.

Dewar and Grisdale's FM method, although an oversimplification, may be considered an improvement since it is an attempt to include both conjugative and non-conjugative effects in a single model. Its success in predicting substituent effects in aromatic systems is encouraging, and its failure in the alicyclic systems emphasizes that polar, resonance, and steric interactions must all be carefully considered in a prediction or interpretation of substituent effects.

The results of the recent MO calculations are a very interesting new development, although there is not yet much experimental verification of the predicted alternating effects. Ehrenson<sup>1</sup> suggested that the field effect model may be improved to encompass the inductive effect model. He proposed that if one could obtain a good charge density diagram from wave functions for the molecule which included inner and peripheral solvation effects, then interactions along directions having high electron density, normally the molecular framework, could be viewed as



differing only in degree from interactions through space or solvated space, where the electron density should usually be smaller.

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# THE MECHANISM OF COMPLEX-CATALYZED HYDROSILATIONS

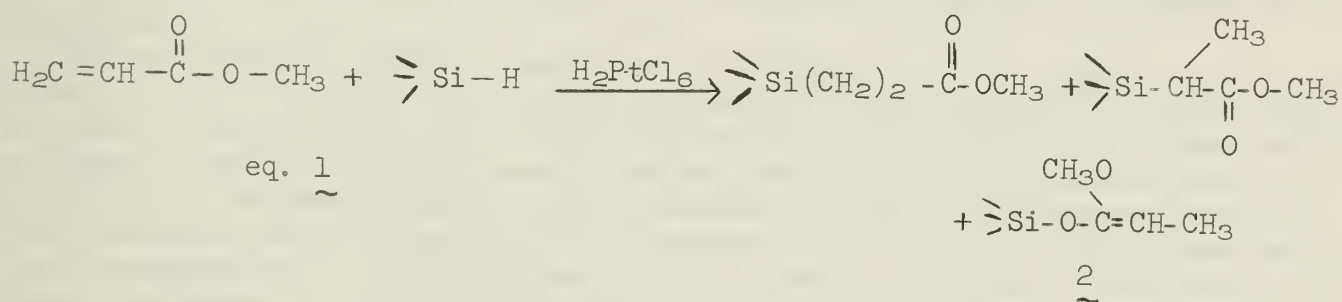
Reported by Harold Bruner

May 6, 1968

Hydrosilation is the addition of the two termini of a silicon-hydrogen bond across an unsaturated position. The reaction may be run by heating the two reactants under pressure, but in most cases a catalyst is used. Peroxides, ultraviolet light, Lewis acids, Lewis bases, and some Group VIII metals and their complexes have been used with varying degrees of success. Hydrosilations catalyzed by Group VIII metal complexes are often accompanied by extensive isomerization of the olefin. A strong preference exists for the addition of the silyl group on the terminal primary carbon regardless of the initial position of the double bond. These unusual results have prompted extensive mechanistic studies. This seminar will review this work. Much of the early work was thoroughly reviewed<sup>1,2</sup> and will only be briefly mentioned here.

## HYDROSILATION

From the start, workers noted that for all nonconjugated linear olefins, a strong preference existed for the formation of n-alkylsilanes in the complex-catalyzed hydrosilation reaction regardless of the initial position of the olefinic bond. Both 1-pentene and 2-pentene react with trichlorosilane in the presence of chloroplatinic acid to form only n-pentyltrichlorosilane<sup>3</sup>. The nonterminal adducts were independently synthesized and found not to rearrange, even when heated for prolonged periods in a sealed glass tube at 100°C in the presence of chloroplatinic acid and trichlorosilane. The process appeared to be dependent upon the nature of the silane. When 3-hexene was treated with trichlorosilane and chloroplatinic acid, only the n-hexyl isomer was observed, but treatment with sym-dimethylsiloxane under approximately the same conditions, yielded the 1-, 2-, and 3-hexyl adducts<sup>4</sup>. When conjugation was present, several modes of addition were observed. Styrene formed both 1- and 2-phenylethylsilanes<sup>5</sup>. Methyl acrylate, 1, afforded 2- and 3-silylpropionic esters and the vinyl silyl ether, 2<sup>1,6</sup>.



Another process common to the complex-catalyzed hydrosilation reaction is olefin isomerization. When excess olefin is recovered from the reaction or when the reaction is prevented from going to completion, the olefin is generally present as a mixture of isomers with concentration determined by the relative thermodynamic stabilities under the reaction conditions. Selin and West<sup>7</sup> demonstrated that the reaction of either excess 1-methylcyclohexene or 4-methylcyclohexene with trichlorosilane and chloroplatinic acid resulted in the recovery of the same equilibrium mixture of olefins. Attempts to isomerize olefins under hydrosilation conditions in the absence of either the catalyst or the silicon hydride were unsuccessful.<sup>7,8</sup> No isomerization was observed upon treatment with chloroplatinic acid and silicon tetrachloride.<sup>7</sup>

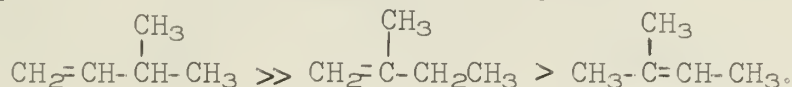
## EARLY KINETIC STUDIES

Mechanistic studies of this reaction have been greatly hindered by the lack of meaningful kinetic data. The only quantitative kinetic study available is that of Reikhefel'd and Grigor'eva<sup>9</sup> who caused a series of polymers,  $[(\text{Me}_2\text{SiO})_{5-7}\text{MeHSiO}]_n$  ( $n=1,4$ , or  $5$ ) to react with styrene, methylmethacrylate, and allyl cyanide. The rate was found to be independent of polymer concentration, and to increase with chloroplatinic acid concentration and in an inert atmosphere. First-order kinetics were observed. These workers postulated a mechanism involving heterogeneous catalysis.



They proposed the formation of an intermediate complex between the olefinic  $\pi$ -electrons and the d-orbital of silicon on the surface of the colloidal platinum formed by the reduction of chloroplatinic acid by silane. The higher rate and lower activation energy observed for the reaction of the more electron-rich olefin,  $\alpha$ -methylstyrene, with polysiloxane than that for the reaction with methylmethacrylate supports the  $\pi$ -complex portion of their proposal.

Competition reactions have been attempted by two groups. Ponomarenko and co-workers<sup>10</sup> observed that ethylene becomes less reactive as more fluorine substituents are added, but also noted a drop in rate when electron-donating substituents were present. Saam and Speier<sup>8</sup> studied a series of methylbutenes and observed the following order of reactivity:



Both groups concluded that more electron-rich olefins reacted faster, but additional substituents create a steric hindrance to reaction. Ponomarenko also studied competitive reactions between silanes<sup>10-12</sup>, and although some of the same steric and electronic effects could be observed, the meaning of the results was uncertain since several reactions were observed in which silane became more reactive when placed in a reaction medium with another silane also present.

#### EARLY MECHANISTIC PROPOSALS

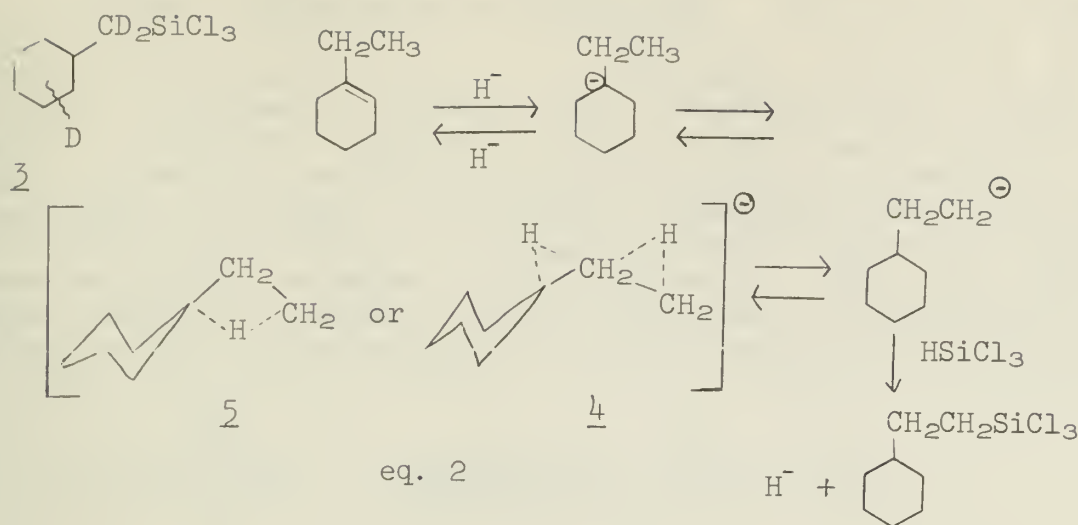
Benkeser and coworkers<sup>13-15</sup> studied the hydrosilation of alkynes. No rearrangements were observed and monoadducts resulting from the addition of the silyl group to both ends of the triple bond were formed.<sup>15</sup> Stereospecific cis addition was observed with both chloroplatinic acid and platinum-on-carbon as catalysts<sup>14</sup>. The workers suggested that the black solid which formed in their reaction with chloroplatinic acid, was finely divided platinum metal (generated by the reduction of the acid by silicon hydride) coating small silicone particles (formed from polymerization of the silane) suspended in the solution. The platinum metal then acted as a catalyst by adsorption and activation of silane in a manner analogous to platinum-catalyzed hydrogenations.

Selin and West<sup>7</sup> studied a series of 1-alkylcyclohexenes. Adducts were observed to form both at the end of the alkyl chain and on the ring when the alkyl chain was a maximum of two carbons long. When chlorosilanes and alkylchlorosilanes were added, the adduct on the alkyl chain was the major product with much lower yields of the ring adduct. The same products were obtained if 4-alkylcyclohexenes were used, and if the reactions were stopped prior to completion, the 4-alkylcyclohexene was found to have rearranged to a 50% mixture of the 1- and 4- isomers. Replacement of the tertiary hydrogen by a methyl group with 4,4-dimethylcyclohexene resulted in the formation of only ring-substituted product. When 1-methyl- $d_3$ -cyclohexene was reacted, the same adducts formed as with undeuterated olefin, and there was no deuterium exchange. A large kinetic isotope effect was observed, indicating an intramolecular proton shift concurrent with the rate-determining step. Unfortunately, it could not be determined to which ring carbon the deuterium was attached in the terminal silane, 3. When three carbons or more were present in the alkyl chain, the compounds were essentially unreactive, giving no adduct formation and less than 5% isomerization. The authors postulated the carbanion mechanism in eq. 2, in which the carbanion and two adjacent carbons occupied a reaction site in a complex with the catalyst. The catalyst, in some unspecified manner, then facilitates a proton transfer over a 2 carbon distance by either two 1,2 proton shifts (4) or one 1,3 shift (5). The carbanion intermediate must be able to either produce primary carbanion for reaction with silane or to reform olefin. One weakness of this mechanism is that the hydride ion would have to add in a manner inconsistent with the polarity of the double bond in order to form a tertiary rather than a secondary carbanion.



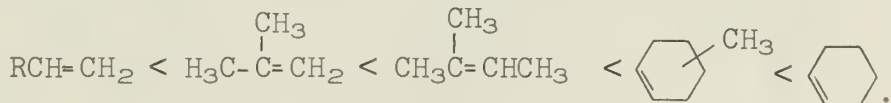





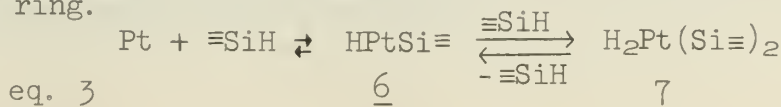


Ryan and Speier<sup>16</sup> permitted deuteriosiloform ( $\text{DSiCl}_3$ ) to react with a series of olefins in the presence of chloroplatinic acid. The solutions remained clear and colorless throughout the reactions, arguing against Benkeser's proposal of heterogeneous catalysis. They found that deuteriosiloform and dichloromethylsilane exchanged protons readily at room temperature with even trace amounts of chloroplatinic acid. Without catalyst, no exchange occurred even at  $100^\circ \text{C}$ . Deuteriosiloform added to olefins to give deuterated products. The reaction of 2-methylpropene and deuteriosiloform yielded  $\text{Cl}_3\text{SiC}_4\text{H}_{6.5}\text{D}_{2.5}$  plus a mixture of deuterated and nondeuterated siloform. In the adduct the tertiary carbon was 70% deuterated and the other carbons contained an average of 1.8 deuteriums per molecule. The deuterated adduct did not exchange deuterium when added to the reaction mixture of 1-octene with excess siloform. When the reaction was run with excess olefin and deuteriosiloform, the recovered olefin did ~~not~~ contain deuterium. The authors explained these results by invocation of a mechanism for homogeneous catalysis. Chloroplatinic acid is first reduced by silicon hydride as in eq. 3. Either adduct 6 or 7 might serve as the addition catalyst. Through the equilibrium between 6 and 7, deuteriosiloform and dichloromethylsilane exchange hydrogen. The olefin then adds reversibly to either 6 or 7 and thusly is deuterated and isomerized. The formation of secondary and tertiary alkyl platinum derivatives is a rapid, but readily reversible reaction.

Thus, nonterminal olefins, which react to form these derivatives, are more extensively isomerized and deuterated. Primary alkyl platinum adducts tended to decompose irreversibly to the primary alkylsilane and not exchange with deuterium. Ryan and Speier observed that the degree of isomerization was inversely proportional to the ease of formation of the alkylsilanes. Deuterium substitution increased in the order:

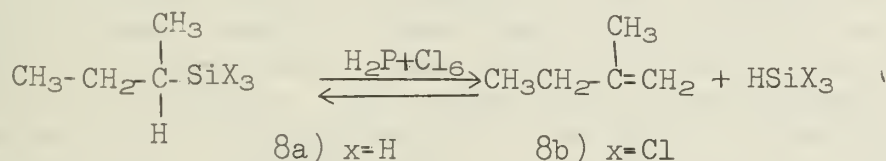


The lack of deuterium exchange reported earlier for 1-methyl-d<sub>3</sub>-cyclohexene was believed to be a result of an intramolecular hydrogen transfer caused by the relatively high energy olefin (CD<sub>2</sub> ) that would be the intermediate in the formation of adduct. This argument is weakened by the studies of Herling and coworkers<sup>17</sup> on the isomerization of methylcyclohexenes over sodium-alumina catalyst at 25° C. Although the methylenecyclohexane is the highest energy olefin, it is present in approximately 10% of the concentration of the 3- and 4- methylcyclohexenes. The difference in energy is, therefore, not very large. Ryan and Speier observed extensive deuterium exchange with deuteriosiloform and 1-methylcyclohexene, but could not determine the positions of deuteration on the ring.





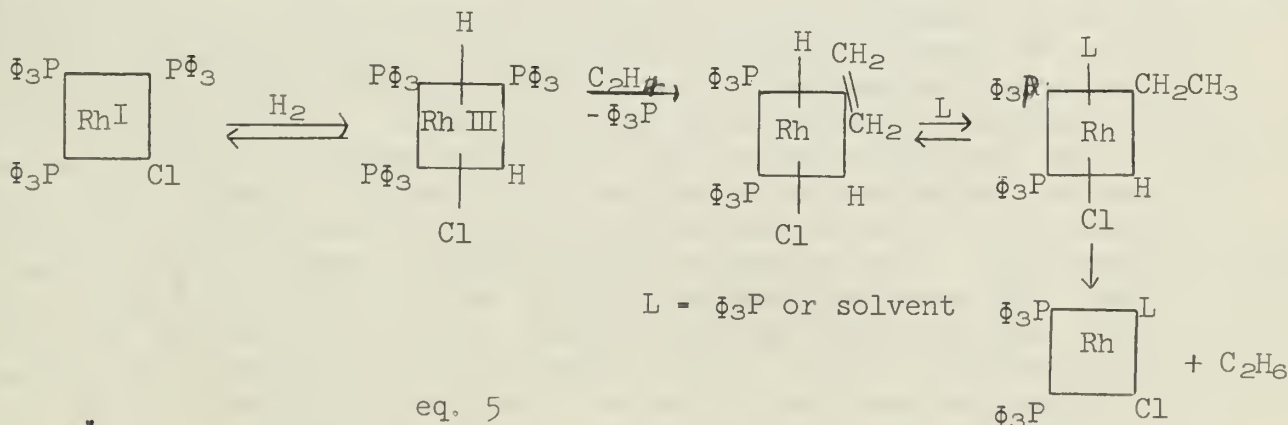
The recent finding of Spialter and O'Brien<sup>18</sup> support the premise that the formation of primary alkylsilanes is irreversible. These workers prepared (+)-(s)-2-methylbutylsilane (8a) and (+)-(s)-2-methylbutyltrichlorosilane (8b). If the reverse reaction in hydrosilation (eq. 4) occurred with a significant rate and the reactants were able to separate in solution, then the adduct should racemize under normal reaction conditions. Only small changes in  $[\alpha]_D^{20}$  were observed ( $< .23^\circ$ ) with a variety of reaction temperatures which the authors believed to be within the range of experimental uncertainty. To encourage racemization the earlier reactions were rerun in the presence of 2-methyl-1-butene which could compete for silane with olefin stereospecifically oriented on the metal complex. The authors also ran the hydrosilation reaction of 2-methyl-1-butene with excess siloform with the optically active adduct present in the reaction mixture. In both reactions no isomerization was observed.



eq. 4

#### THE CHALK-HARROD MECHANISM

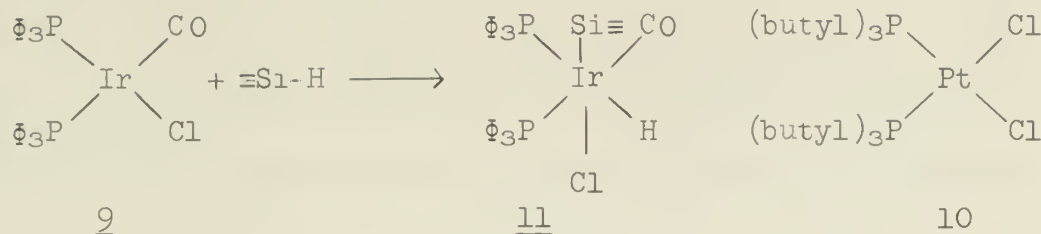
Chalk and Harrod ran a series of investigations<sup>19a-f</sup> to determine the complex serving as the catalyst in hydrosilation. These workers approached the problem assuming that catalysis of hydrosilation operated by a mechanism similar to that proposed for other homogeneous reactions catalyzed by Group VIII metal complexes, such as hydroformylation or homogeneous hydrogenation. The mechanism for this latter process is summarized in eq. 5, for the case of  $\text{RhCl}(\text{P}\phi_3)_3$  and ethylene<sup>25</sup>. The complex adds hydrogen (formally an oxidation). Either before or after the hydrogen adds, the olefin displaces one ligand and forms a  $\pi$ -complex, which can rearrange to a  $\sigma$ -bonded complex with the addition of one of the hydrogens to the weakened double bond. This  $\pi$ - to  $\sigma$ -bonded complex transition has been shown to proceed with cis-addition of metal and hydrogen<sup>21,27</sup> to the double bond. The octahedral complex can then decompose thermally to the more stable square planar form, eliminating ethane. The effectiveness of a catalyst is determined by both the ease of formation of the octahedral complex and the subsequent thermal instability of the octahedral complex.



Several octahedral complexes formed via addition of hydrogen to square planar complexes, have been found to be of sufficient thermal stability to allow isolation and identification<sup>27</sup>; one such compound is bis(triphenylphosphine)chloriridium (I) carbonyl, 9. Chalk and Harrod prepared bis(tributylphosphine)dichloroplatinum (II), 10, and 9, and allowed these to react with several silanes.

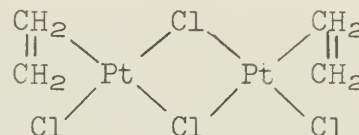






The only reactions observed with 10 were metathetical exchange with trialkyl- and triarylsilanes with the formation of the trialkyl- or triarylchlorosilane. With 2, adducts formed readily at room temperature with all silicon hydrides except trialkyl- or triarylsilanes. The weight increase of the isolated adducts, 11, corresponded to 1:1 addition. When these adducts were heated in a vacuum, the material was reduced to its original weight. The need for the Si-H bond was shown by the failure of silicon tetrachloride to form adducts below 50°. The probable structure of the adduct was obtained from the infrared spectra. The carbonyl stretching frequency has been shown to be a very sensitive measure of the electron density on the central metal atom. As the oxidation state of the metal is increased, the amount of backbonding between the metal d orbitals and the  $\pi^*$  molecular orbital in the carbonyl decreases and the frequency of the carbonyl stretch increases. Observations of the carbonyl band in 11 and 2 show a rise of 25 to 85  $\text{cm}^{-1}$  in the frequencies of the adduct, implying that Ir(I) has been oxidized in some manner. A band corresponding to the Ir-H stretch also appeared in the spectra of the adducts.

Chalk and Harrod<sup>19-b</sup> discovered that Pt(II) olefin complexes such as 12 gave almost the same rate, yield, and products as chloroplatinic acid, indicating the catalytic ability to be a function of the metal ion. These workers used this olefinic complex for kinetic studies of reactions between several silanes and 1-hexene. Their kinetic data were not highly reproducible, and it was suggested that this was a result of impurity interference at the very low catalyst concentration ( $10^{-6}\text{M}$ ) at which the reaction must be run to remain isothermal. The rate effect of impurities was demonstrated by Benkeser, *et. al.*, when they observed that whereas no diadduct often formed in the hydrosilation of alkynes with freshly-prepared chloroplatinic acid, the diadduct would form in good yield with chloroplatinic acid which had been allowed to stand for two days.



12

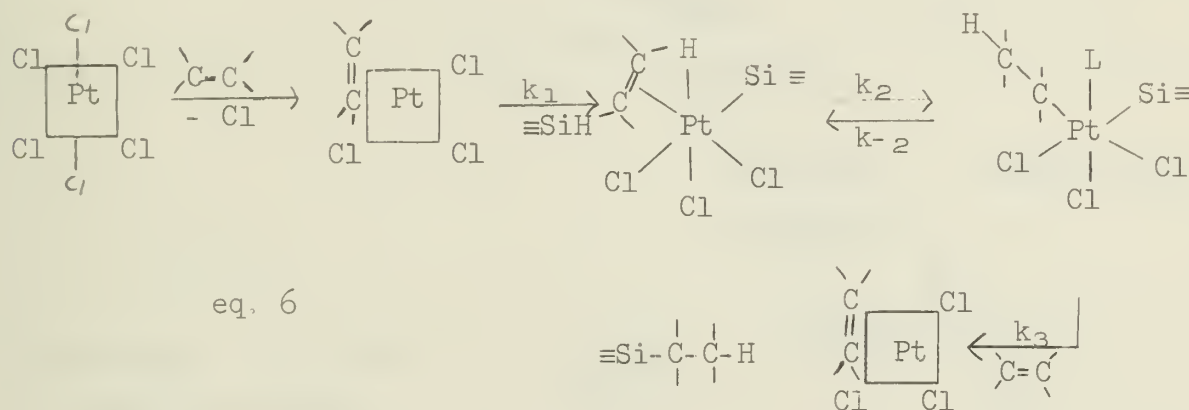
Upon studying their kinetic data the authors determined the existence of three classes of hydrosilations. When triethoxy- or trimethoxysilanes were added to 1-hexene, the additions occurred rapidly in greater than 90% yield and no isomerization of olefin was observed. The solution remained clear throughout the reaction. With trialkyl and triarylsilanes, the hydrosilation and isomerization reactions initially went rapidly, but the rates of both quickly dropped to zero. The reaction mixture rapidly became dark brown, and the yield of adduct were under 20%. Better yields were obtained when the reaction was run slowly using chilled solutions. The platinum complex had been reduced to platinum metal in the highly exothermic reaction and had resulted in deactivation of catalyst. Palladium complexes are readily reduced to the metal by most silanes and were inactive as catalysts. Heterogeneous catalysis thus seems very unlikely under these conditions. When any other silane is reacted with 1-hexene and Pt(II) complex, the third reaction type was observed. Isomerization and hydrosilation occur simultaneously. The reaction darkens very slowly, but the decreased yields of adducts (50-80%) appear to be more a result of the longer reaction times than of catalyst deactivation.

Phenyldichlorosilane was added to  $10^{-6}\text{M}$  Pt(II) and kinetic studies of isomerization were run<sup>19-b</sup>. No autocatalysis was observed and it was suggested that silane



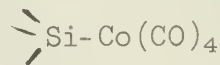
reacted with the complex to produce the catalyst for isomerization. With insufficient silane present, the olefins did not reach the relative concentrations predicted by their thermodynamic stabilities. The addition of more Pt(II) catalyst did not change the distribution of olefin isomers. Upon addition of silane, further isomerization occurred. For every mole of silane adduct formed, approximately two moles of olefin isomerized. When the same tests were run with triethylsilane, five moles isomerized per mole of adduct.

Chalk and Harrod explained the data with the mechanism depicted in eq. 6.



The mechanism is completely analogous to the homogeneous hydrogenation mechanism. When silicon is substituted with highly electron-withdrawing groups,  $k_3$  becomes greater than  $k_{-2}$  and isomerization decreases. The hydrosilation process must also be faster than the irreversible reduction of the complex to the metal for the catalyst to be successful.

If this mechanism is correct, some other homogeneous catalysts should be effective in hydrosilation. Iron pentacarbonyl<sup>23</sup> has been used as catalyst here, but side reactions limit its efficiency. Harrod and Chalk<sup>19-d</sup> found that dicobaltoctacarbonyl, a hydroformylation and hydrogenation catalyst was also a good hydrosilation catalyst. The only difference observed between platinum-catalyzed and cobalt-catalyzed hydrosilations was the presence of considerably more isomerization in the latter case. Isomerization of 1-hexene was observed with all olefins tested, including the trialkoxysilanes. When dicobaltoctacarbonyl is added to the pure silane<sup>19-e</sup>, an equivalent of hydrogen is released and two equivalents of the silylcobalt tetracarbonyl complex, 13, form. Addition of olefin to a solution of 13 resulted in no adduct formation or isomerization. When the reaction was run at  $-60^\circ$ , the cobalt hydrocarbonyl could be isolated. This latter compound was found to decompose at room temperature to hydrogen and cobalt octacarbonyl. During the reaction, the infrared bands corresponding to both the Si-H and the bridge carbonyl disappeared.



13

Chalk and Harrod<sup>19d,f</sup> ran several rate studies on cobalt-catalyzed hydrosilations. Although the results were again not highly reproducible, certain observations could be made. The rates of both isomerization and hydrosilation were greatest when olefin was present in excess and dropped rapidly if silane concentration was increased over that of olefin.<sup>19d</sup> Although the absolute rates varied considerably from one olefin-silane system to another, the rate of isomerization remained approximately twenty times faster than hydrosilation.

By analogy to other homogeneous catalytic reactions of dicobalt octacarbonyl<sup>20, 24</sup> Chalk and Harrod proposed the mechanism in Figure 1. The initial reaction has been shown to occur in  $\text{Co}_2(\text{CO})_8$  reactions with hydrogen<sup>25</sup> and the isolation of cobalt hydrocarbonyl from this reaction mixture proves that this step is present. The failure of 14 to catalyze hydrosilation indicates that the hydrocarbonyl is the catalytic species. The cobalt hydrocarbonyl can react with excess silane to form the inactive 14 or can react with olefin to form the alkylcobalt adduct 15. This reaction





undoubtedly proceeds through the  $\pi$ -bonded intermediate 16, which can then rearrange to the  $\sigma$ -bonded complex 15. Compound 15 may then react with silane to form product. In view of the relatively high rate of isomerization, this last addition reaction is probably the rate-determining step.

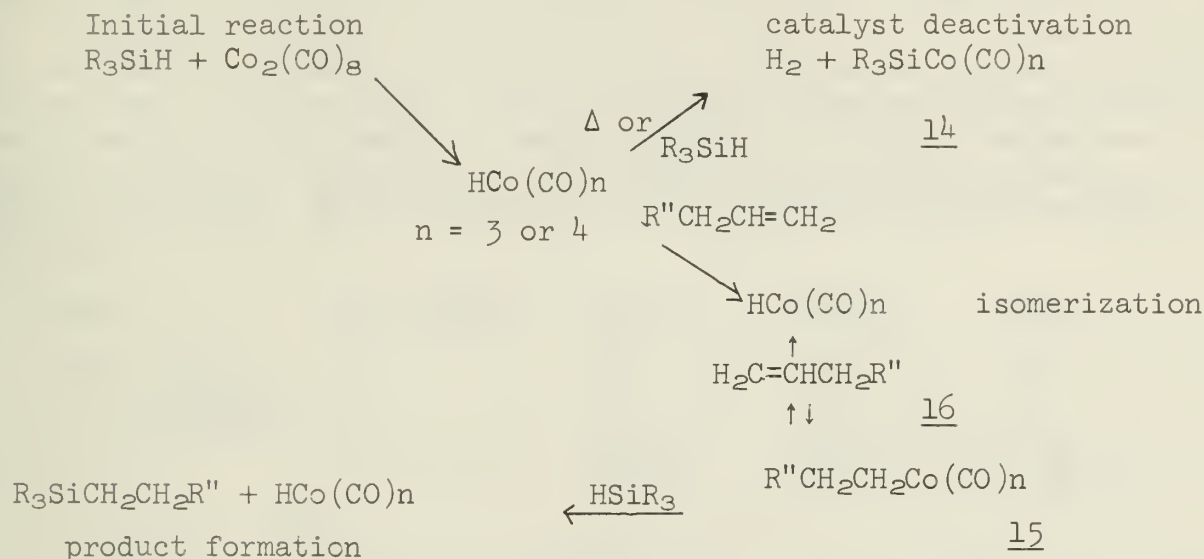


Figure 1

Chalk and Harrod<sup>19c,f</sup> also investigated the problem of 1,3 vs. 1,2 hydride shifts in isomerization of olefin. A 1,3-shift would involve a  $\pi$ -allylic intermediate (17) while a 1,2 shift would involve a  $\sigma$ -intermediate (18). These authors reacted 1-heptene-3- $d_2$  with small amounts of silicon hydrides and cobalt octacarbonyl. The distribution of hydrogen in 1-heptene-3- $d_2$  is given in Table 1. A coisomerization of 1-pentene and 1-heptene-3- $d_2$  was performed. The infrared spectrum contained bands corresponding to deuterium substitution at every carbon in the allylic system of pentene. Since 17 would produce substitution only at the ends of the allylic system, intermediate 18 was assumed to be the correct one.

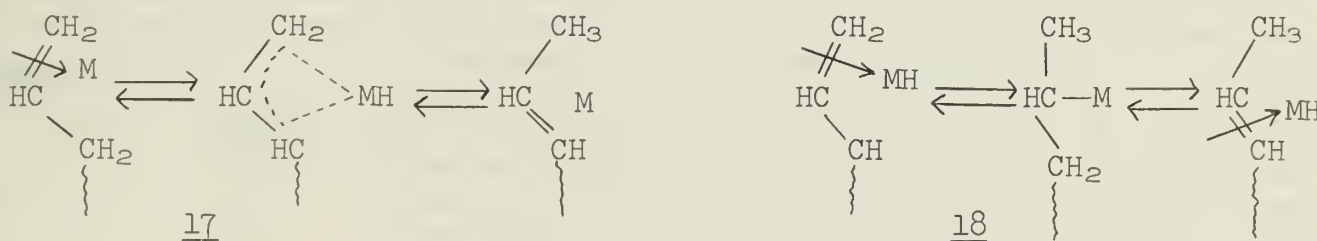


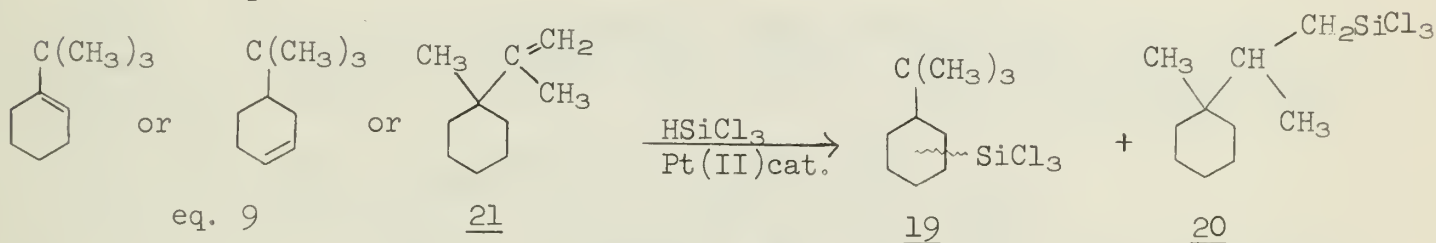
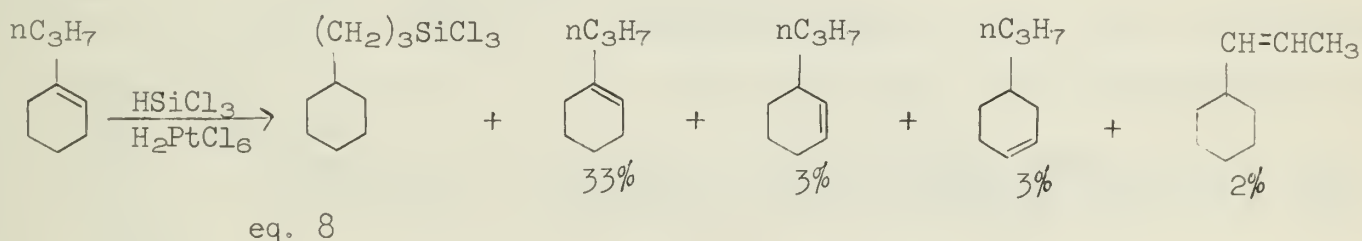
Table I - Deuterium Exchange Study

Time (min.)	Number of Hydrogens by NMR ( $\pm .1$ )			mole % 1-heptene-3- $d_2$
	-CH <sub>2</sub>	-CH-	-CH <sub>2</sub> C=	
0	2	1	0	100
12	0.7	0.65	1.00	40
24	0.32	0.43	1.46	25

The work of Selin and West<sup>7</sup> with 1-alkylcyclohexenes is difficult to explain by the Chalk-Harrod mechanism. These workers observed isomerization only to 1- and 4-alkylcyclohexenes and obtained no hydrosilation products when the alkyl chain was more



than three carbons long. Benkeser and coworkers<sup>25</sup> reexamined this work. If siloform (rather than 1-n-propylcyclohexene) is present in excess. The reflux temperature increases and both addition and isomerization occur. All possible isomers were observed except propylidenecyclohexane and allylcyclohexane. When similar studies were attempted using each possible isomer of ethylcyclohexene as the substrate, the products were in all cases the terminal alkyl adduct, trace amounts of ring adducts, and a mixture of olefins containing every possible isomer except vinylcyclohexane. The lack of the vinyl and allylcyclohexanes is easily explained by the high reactivity of these olefins toward silane in hydrosilation reactions. Benkeser and Cunico<sup>30</sup> discovered the first example of alkyl migration in isomerization when they reacted 1- or 4-t-butylcyclohexene with trichlorosilane and Pt(II) catalyst. They identified adducts 19 and 20. When 21 was the initial olefin, the same two adducts were again obtained.



The observation by Selin and West<sup>7</sup> that 1-methyl-d<sub>3</sub>-cyclohexene gives the terminal silane adduct without deuterium exchange has been verified<sup>16</sup>. The Chalk-Harrod mechanism would predict ring deuteration as in 22. However, since a large amount of deuterium was found to be incorporated into 1-methylcyclohexene upon treatment with deuteriosiloform<sup>16</sup>, some deuterium exchange might be expected in Selin and West's study through the intermediate 23. Although an explanation might be made involving an unusually rapid, irreversible formation of the terminal σ-bonded alkylmetal derivative, this must be considered an embarrassing result for the Chalk-Harrod mechanism.

Sommer, Lyons, Fujimoto, and Michael<sup>27, 28</sup> recently studied the hydrosilation reaction with optically active (+) α-naphthylphenylmethylsilane, 24. When 24 reacted with inactive deuterophenylethylmethylsilane and chloroplatinic acid, extensive deuterium-hydrogen exchange occurred. The (+)-deuterophenylethylmethylsilane was formed with 100% retention of configuration. When the optically active, deuterated silane was reacted with hydrogen gas with catalyst present, 24 was reformed with 100% retention of configuration<sup>28</sup>. When 24 reacted with 1-octene with either chloroplatinic acid or tetraethylene-μ, μ'-dichlorodiplatinum (II), the adduct formed with 89-100% retention of configuration<sup>27</sup>. These results support the Chalk-Harrod mechanism provided that the insertion of the platinum atom into the silicon-hydrogen bond and the formation of product from the σ-complex proceed with retention of configuration at the silicon center.

## SUMMARY

Hydrosilations catalyzed by Group VIII metal complexes have been shown to yield primarily terminal adducts. This occurs as a result of the addition of silane and olefin to the complex and subsequent equilibrium between σ- and π-bonded forms of the complex until a primary σ-alkylmetal adduct is formed. This compound will then react with silyl ligand to form the organosilane. At any point during the π bond migration





the complex may release the isomerized olefin. The addition has been shown to proceed with cis-addition and retention of configuration about the silicon atom. The Chalk-Harrod mechanism appears able to explain most of the available data.

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# TERTIARY HYPOHALITE HALOGENATIONS

Reported by Richard J. Arhart

May 9, 1968

## INTRODUCTION

Alkyl hypohalites have been known since 1875.<sup>1</sup> Primary and secondary alkyl hypochlorites decompose rapidly at room temperature and explode in strong light. The decomposition products of primary hypochlorites are chiefly hydrogen chloride and aldehydes while those of secondary hypochlorites are hydrogen chloride and ketones.<sup>1-4</sup> Little mechanistic work has been done on primary and secondary hypohalites and therefore only the more stable tertiary hypohalites will be considered here. This seminar will be concerned primarily with the free radical halogenation of a variety of hydrocarbons by tertiary hypohalites. The mechanism of the halogenation will be examined with regard to selectivities of the alkoxy radicals involved as intermediates, competitive intramolecular decomposition of the alkoxy radicals vs. inter- and intramolecular hydrogen abstraction, relative reactivities of hydrocarbon hydrogens, solvent effects, and kinetics of the overall reaction.

## PREPARATION, PROPERTIES, AND DECOMPOSITION OF HYPOHALITES

Organic hypochlorites may be prepared by passing chlorine gas through aqueous, alkaline solutions of the corresponding alcohols at 0° in the dark.<sup>5</sup> Other satisfactory methods include treatment of the alcohol with chlorine monoxide or aqueous hypochlorous acid.<sup>1</sup> Attempts to prepare *t*-butyl hypobromite or iodite from halogen, base, and *t*-butyl alcohol yield no product. However, reaction of *t*-butyl alcohol with aqueous hypobromous acid gives the hypobromite in 42% yield.<sup>6</sup> *t*-Butyl hypoiodite has been prepared recently by the addition of a suspension of mercuric iodide (1 mole) to a carbon tetrachloride solution of *t*-butyl hypochlorite (2 moles).<sup>7</sup>

*t*-Butyl hypochlorite is sufficiently stable to be purified by distillation at 79.6° under atmospheric pressure. If kept cold and dark, *t*-butyl hypochlorite may be stored for long periods without appreciable decomposition. *t*-Butyl hypochlorite can be heated without change in blackened blubs up to 4½ hours at 90°.<sup>8</sup> Consequently, the generally accepted notion that *t*-butyl hypochlorite is thermally unstable may not be entirely correct; possibly light is necessary for decomposition at moderate temperatures. Decomposition of *t*-butyl hypochlorite in the vapor phase yields acetone and methyl chloride. *t*-Butyl hypobromite is stable in the dark at 0° for long periods, but decomposes upon heating to 85° or upon irradiation to give acetone and methyl bromide.<sup>6</sup>

The decomposition of hypochlorites is inhibited by free radical inhibitors such as oxygen and 2,4,6-tri-*t*-butyl phenol and enhanced by light and free radical initiators such as azobisisobutyronitrile. The free radical mechanism for decomposition is shown in scheme I.<sup>9</sup> Gray and Williams<sup>3</sup> have estimated  $\Delta H = 5$  kcal/mole

### Scheme I

- 1)  $R_3COCl \rightarrow R_3CO\cdot + Cl\cdot$
- 2)  $R_3CO\cdot \rightarrow R_2CO + R\cdot$
- 3)  $R\cdot + R_3COCl \rightarrow RCl + R_3CO\cdot$

and  $E_a = 13$  kcal/mole for the beta scission of the alkoxy radical in step 2. In the presence of a hydrogen-containing substrate hydrogen abstraction by the alkoxy radical to form the corresponding alcohol and an alkyl radical competes with the beta scission of step 2.

The decomposition of *t*-butyl hypochlorite in carbon tetrachloride is much slower than the decomposition in the gas phase. The slowness of the beta scission process allows a number of other reactions to compete. Upon irradiation of a 2.1M *t*-butyl hypochlorite solution in carbon tetrachloride at 0°, Walling and Padwa<sup>10</sup> obtained the following approximate yields of major products by gas chromatographic analysis: acetone (17%), *t*-butyl alcohol (62%), isobutylene oxide (2.6%), chloroacetone (3%), and chloro-*t*-butyl alcohol (22%). Methyl chloride was observed but was not measured quantitatively. When the decomposition was carried out under the same conditions





except the temperature was raised to 80°, the yield of acetone and *t*-butyl alcohol was 50% and 27%, respectively. Upon dilution with carbon tetrachloride the acetone yield increased. Higher temperatures enable the beta scission process to compete more effectively with the lower energy activation process of hydrogen abstraction.

Greene and co-workers<sup>9,11</sup> decomposed a number of tertiary hypochlorites both by thermal initiation at 80° and photochemical initiation at 0° in aprotic solvents. The thermal decomposition of methylethylisopropylcarbinyl hypochlorite yielded isopropyl chloride and methyl ethyl ketone in 95% yield, ethyl chloride and methyl isopropyl ketone in 3% yield, and methyl chloride and ethyl isopropyl ketone in less than 0.5% yield. From this example and several others it was concluded that the order of increasing ease of fragmentation of alkyl groups is methyl < primary alkyl < secondary < tertiary.<sup>11</sup> This order of fragmentation is in the order of increasing radical stability or simply increasing size. The photochemical decomposition of dimethyl-1-norbornylcarbinyl hypochlorite afforded 1-chloronorbornane and acetone in 22% yield and methyl 1-norbornyl ketone in 5.2% yield. The preference for elimination of the fairly unstable tertiary 1-norbornyl radical vs. elimination of methyl is only four to one. The order of fragmentation then appears to be more dependent upon the stability than the size of the departing group.

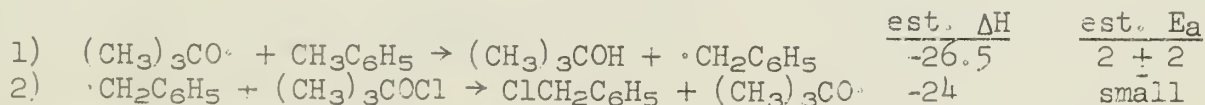
Greene and co-workers<sup>12</sup> decomposed dimethyl(*cis* and *trans* -4-*t*-butylcyclohexyl)carbinyl hypochlorite in carbon tetrachloride in the temperature range -80° to 0°. Both *cis* and *trans* starting materials gave practically the same ratio (2:1) of *cis*: *trans*-4-*t*-butylcyclohexyl chloride upon loss of acetone over the entire temperature range. Interestingly there was a slight decrease in selectivity with decreasing temperature. The fact that both the starting *cis* and *trans* hypochlorites gave identical ratios of products indicated that the 4-*t*-butylcyclohexyl radical formed upon loss of acetone was a common intermediate. The surprising feature of the reaction is the preferential formation of *cis* chloride (axial chlorine) over *trans* chloride (equatorial chlorine).

In the decomposition of certain long-chain tertiary hypochlorites, intramolecular hydrogen abstraction competes with cleavage. This process will be discussed later. The principal paths of reaction then available to the alkoxy radical are fragmentation and inter- and intramolecular hydrogen abstraction.

#### HYDROGEN ABSTRACTION FROM CARBON

*t*-Butyl hypochlorite is an efficient free radical chlorinating agent for alkyl, benzylic, and allylic positions of hydrocarbons and derivatives. The over-all reaction is  $RH + t-BuOCl \rightarrow RCl + t-BuOH$ . Walling and Jacknow<sup>13</sup> observed that 3:1 mixtures of *t*-butyl hypochlorite:toluene were stable for long periods under nitrogen in the dark, but when initiated by light or a radical initiator showed a rapid reaction after a variable induction period with complete consumption of *t*-butyl hypochlorite. The reaction was inhibited or retarded by oxygen and phenolic materials. The major products were benzyl chloride and *t*-butyl alcohol. Small amounts of benzal chloride, chlorotoluenes, acetone, and methyl chloride were observed. The propagation steps for the radical mechanism are shown in scheme II.

#### Scheme II



The small activation energy for hydrogen abstraction in step 1 compared to that for beta scission ( $E_a = 13$  kcal/mole) accounts for the small amount of acetone formed and contributes to the long chain length of  $10^4$  estimated for the consumption of *t*-butyl hypochlorite through both processes. Practically all of the methyl radicals produced upon beta scission of the *t*-butoxy radical were converted to methyl chloride since only traces of methane were detected. The small amount of ring-substituted chlorotoluenes (less than 2%) formed supports the radical mechanism.

Saturated aliphatic hydrocarbons also undergo rapid photoinitiated chlorination by *t*-butyl hypochlorite.<sup>14</sup> The *t*-butoxy radical shows considerable selectivity in



its attack on C-H bonds, reactivities increasing in the order primary < secondary < tertiary for both purely aliphatic and benzylic C-H bonds. This selectivity is illustrated in Table I, which summarizes a large number of data obtained from competitive studies and isomer distributions.

Table I<sup>15</sup>

Relative Reactivities of C-H Bonds in *t*-Butyl Hypochlorite Chlorination at 40°

	aliphatic	benzylic	allylic <sup>a</sup>
primary	1	10	12 (p,p) 20 (p,s)
secondary	12.2	32	61 (s,p) 93 (s,s)
tertiary	44	69	375 (cyclic; s,s) 176 (t,p)

<sup>a</sup>The symbol (p,p) refers to abstraction of a primary hydrogen with delocalization of the odd electron over an allylic system containing primary carbons at both ends; (p,s) refers to abstraction of a primary hydrogen with delocalization of the odd electron over an allylic system containing a secondary carbon at the other end, etc.

The table shows that in aliphatic as well as benzylic hydrocarbons the order of increasing reactivity corresponds to that of decreasing C-H bond strength in each series. However, when the aliphatic and benzylic series are compared to each other, the bond strength correlation fails. Secondary and tertiary aliphatic C-H bonds with energies of about 94 and 90 kcal/mole are more reactive than benzylic C-H with an energy of 77.5 kcal/mole.

Relative reactivities of two hydrocarbons toward *t*-butoxy radicals can be determined by both direct and indirect methods.<sup>10,16</sup> The direct method involves the measurement of the disappearance of each hydrocarbon relative to an inert internal standard by comparison of gas chromatographic peak areas. The indirect method determines the ratio of hydrogen abstraction to beta scission of the *t*-butoxy radical ( $k_a[RH]/k_d$ ) by measuring the *t*-butyl alcohol/acetone ratio by gas chromatography for each hydrocarbon. The two ratios then give the relative reactivities of the two hydrocarbons indirectly:  $(k_{a1}/k_d)/(k_{a2}/k_d) = k_{a1}/k_{a2}$ .

Wagner and Walling<sup>16</sup> observed that the two methods gave good agreement for systems involving purely aliphatic C-H bonds but poor agreement when aliphatic and benzylic C-H bonds were compared or when two aromatic compounds, one or both of which had nonbenzylic C-H bonds, were compared. In order to study direct and indirect measurements of reactivity, Wagner and Walling treated mixtures of cyclohexane and toluene in chlorobenzene with *t*-butyl hypochlorite at 40°.<sup>16</sup> The concentrations of toluene (0.10M) and hypochlorite (0.02M) were kept constant while the cyclohexane concentration was varied. The amounts of alcohol, acetone, and alkyl chlorides

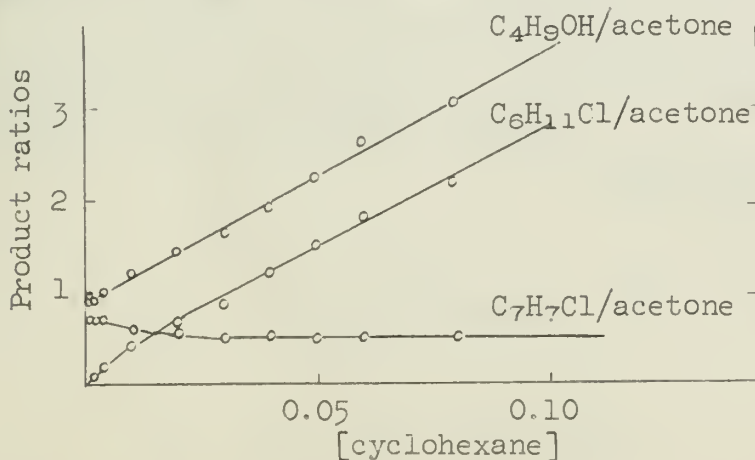


Figure 1. Effect of added cyclohexane on product ratios: 0.02 M *t*-butyl hypochlorite-0.10 M toluene in chlorobenzene at 40°.

formed were measured by gas chromatography. Ratios of alcohol and alkyl chlorides to acetone (all measures of  $k_a[RH]/k_d$ ) were plotted against the initial concentration of cyclohexane as shown in figure 1. Attack on solvent is a constant factor which does not affect the results. Figure 1 shows that addition of cyclohexane lowers the benzyl chloride/acetone ratio to about  $\frac{2}{3}$  its initial value at cyclohexane concentrations above 0.03 M. The slope of the *t*-butyl





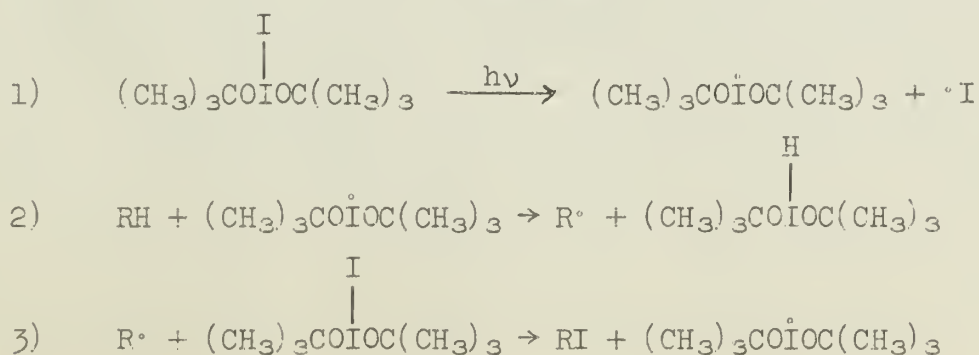
alcohol/acetone plot remains constant. The slope of the cyclohexyl chloride/acetone plot rises sharply while the benzyl chloride/acetone value drops, and after the benzyl chloride/acetone plot has leveled off assumes the same value as that of the slope of the alcohol/acetone plot. These results are inconsistent with the simple hydrogen abstraction mechanism of scheme II.

It appears that changes in  $k_d$  are not responsible for the results because the plot of the alcohol/acetone ratio vs. cyclohexane concentration is linear. The possible exchange reaction  $\text{PhCH}_2^\bullet + \text{c-C}_6\text{H}_{12} \rightarrow \text{PhCH}_3 + \text{c-C}_6\text{H}_{11}^\bullet$  has been ruled out by deuterium exchange experiments. If the energetically favorable reverse reaction occurred, the production of benzyl chloride would be increased relative to that of cyclohexyl chloride. For this situation the difference between the direct and indirect values for the relative reactivity ratio of cyclohexane/toluene should decrease. However, Wagner and Walling observed that the difference between direct and indirect values increased so that the reverse reaction does not appear to account for the differences here. In addition, small amounts of cyclohexane suppress the formation of benzyl chloride, which is replaced by an equivalent amount of cyclohexyl chloride. Larger amounts have no further effect. Wagner and Walling concluded that *t*-butoxy radical attack on toluene occurs by two paths. One is the simple hydrogen abstraction of scheme II which accounts for approximately  $\frac{2}{3}$  of the reaction and competes normally with beta scission and attack on cyclohexane. The second involves an unknown radical intermediate which normally goes on to benzyl chloride, but may be intercepted by cyclohexane to yield cyclohexyl chloride instead. The interception of the unknown radical intermediate by cyclohexane would account for the discrepancies observed in the direct and indirect measurements of cyclohexane-toluene reactivity. Although other systems have not been examined in detail, the authors assume that the same dual path for benzylic hydrogen abstraction accounts for the other discrepancies observed.

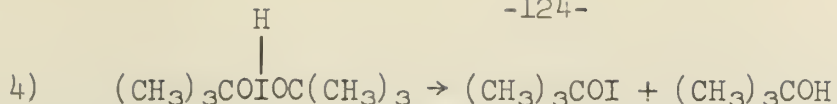
Halogenations with *t*-Butyl Hypobromite and Iodite. A number of competitive brominations of hydrocarbons with *t*-butyl hypobromite has been carried out.<sup>6,17</sup> In each case the reactions paralleled the corresponding chlorinations with *t*-butyl hypochlorite both in selectivity and relative reactivity. This suggests that a free radical mechanism analogous to the hypochlorite case is operative and that the *t*-butoxy radical is the chain carrier.

Tanner and Gidley<sup>7</sup> have recently developed a synthetically useful free radical method for substitution of primary, secondary, and benzylic hydrogens of hydrocarbons by iodine. The method involves irradiation of a mixture of the hydrocarbon and *t*-butyl hypoiodite. The high reactivity of tertiary halide explains the absence of tertiary iodide. The primary:secondary hydrogen selectivity for iodination was approximately 1:29 as compared to that for chlorination 1:12.2. In addition the iodinating reagent showed relative rates of hydrocarbon consumption of 2.5:1 for cyclohexane:2,3-dimethylbutane while the less selective *t*-butoxy radical has a value of 1.9:1.<sup>13</sup> Both the selectivity and the relative reactivity experiments seem to indicate a hydrogen abstracting species which is more selective than the *t*-butoxy radical. The selectivity of the iodinating reagent is reminiscent of that observed in chlorination reactions of iodobenzene dichloride where the  $\text{PhICl}$  radical has been postulated as the abstracting species.<sup>18</sup> The radical chain process in scheme III was proposed for the photoinitiated iodination, where the iodonyl radical is the abstracting species.

### Scheme III







Allylic Hydrogen Abstraction. Walling and Thaller<sup>15</sup> have shown that a variety of olefins react with t-butyl hypochlorite in non-hydroxylic solvents by a photo-induced radical chain process to give good yields of allylic chloride with only small amounts of addition products. Table I illustrates the relative reactivities of allylic C-H bonds. These reactivities depend both upon the degree of substitution of the carbon from which the hydrogen is abstracted and also upon the substitution of the carbon on the other end of the allylic system. As expected the order of increasing reactivity of allylic C-H bonds is primary < secondary < tertiary and (p,s) is more reactive than (p,p), etc. The great relative reactivity of cyclic allylic hydrogens in cyclopentene and cyclohexene may arise from the fact that an entropy loss is incurred by open-chain systems in forming restricted, planar allylic radicals, while in cyclic molecules the system is already frozen.

Stereochemical studies of allylic chlorination with t-butyl hypochlorite have shown that cis and trans-2-butene and 1-butene produce 1-chloro-2-butene and 3-chloro-1-butene by intermediate allylic radicals.<sup>19</sup> However, a common allylic radical is ruled out by the fact that the product ratios are different for each butene. In addition, the 1-chloro-2-butene obtained from trans-2-butene is all trans and that obtained from cis-2-butene is all cis. These results imply that the reaction of allylic radical with t-butyl hypochlorite is much faster than its cis-trans isomerization. A large barrier to free rotation is consistent with the large resonance energy (ca. 25 kcal) calculated for a planar allylic radical.<sup>2</sup> This energy barrier is surmounted, especially at higher temperatures, in certain sterically crowded cis-allylic radicals. For example, cis-2-pentene gives some trans-product at 100°, while cis-4,4-dimethyl-2-pentene gives complete retention only at -78°.

In all the 1- and 2-olefins studied more 1-chloro-2-olefin was formed than 3-chloro-1-olefin. The proportion of the former is greater with more hindered olefins, indicating the importance of steric effects in the transition state for chlorination.

Intramolecular Hydrogen Abstraction. Photoinduced intramolecular 1,5 hydrogen abstraction can occur in a long chain or cyclic hypochlorite in which a quasi-six-membered transition state is possible.<sup>4,20</sup> The major side reaction is beta cleavage, the amount of which is reduced at lower temperatures. The initial product is a  $\delta$ -chloro alcohol which may be cyclized to a substituted tetrahydrofuran by reaction with alcoholic potassium hydroxide. The intramolecular nature of the abstraction step was demonstrated by the fact that an increase in hypochlorite concentration did not change the ratio of  $\delta$ -chloro alcohol to cleavage products. The relative reactivities for intramolecular hydrogen abstraction at 40° are primary: secondary: tertiary; 1:9:47.<sup>4</sup> This result agrees well with the intermolecular chlorination data of Table I where the values are 1:12.2:44.

Solvent Effects. In 1964 Zavitsas<sup>21</sup> chlorinated a number of hydrocarbons in carbon tetrachloride with t-butyl hypochlorite labeled with chlorine-36. In all cases the activity was found exclusively in the alkyl chloride product so that solvent participation in the chain sequence does not occur to any significant extent.

Walling and Wagner<sup>22,23</sup> studied the effect of solvent upon t-butyl hypochlorite halogenations. They observed that aromatic, olefinic, and polar solvents such as acetonitrile and acetic acid affect the reactivity and selectivity of t-butoxy radicals. Changes in the selectivity of hydrogen abstraction appeared in polar solvents while aromatic solvents had little effect. Further, there was no parallel between the ability of aromatic substituents to increase pi electron availability and their effect on selectivity. For example, both benzonitrile and the chlorobenzenes produced larger changes in hydrocarbon reactivity than benzene. The authors concluded that the effects roughly parallel solvent polarity and give little support to any role of charge-transfer phenomena between aromatic solvents and transition states.

The transition state for hydrogen abstraction involves an exothermic, low activation energy process with relatively little bond breaking and bond forming. Accordingly, the transition state should resemble the reactants in structure and any interaction with solvent should be similar in nature to the ground state solvation of the t-butoxy radical, but less in quantity since approach of a t-butoxy radical to hydrocarbon must require displacement of surrounding solvent. The more



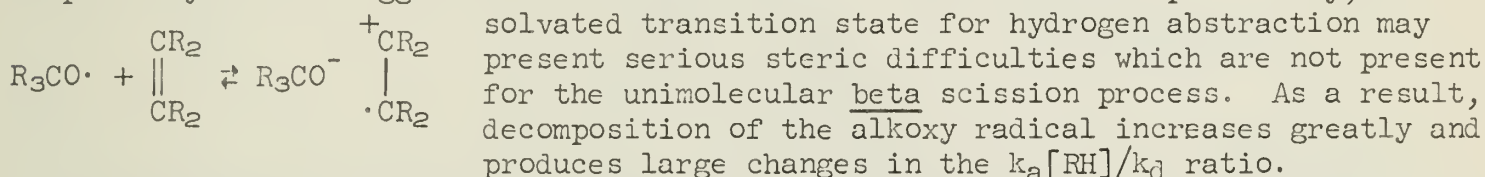




difficult the hydrogen abstraction, the greater the need for a bare unsolvated t-butoxy radical, and the more complete the resulting solvent release.

On the other hand, the transition state for beta scission does not require the close approach of another reactant molecule and, consequently, suffers no steric inhibition of solvation. Further, beta scission is an endothermic, higher activation energy process in which bond breaking to give a relatively polar product is well underway. If the transition state for decomposition is indeed solvated, there could be a decrease in the activation energy requirement so that the rate of beta scission would increase.<sup>23</sup> This increase in  $k_d$  would explain the large solvent effects observed for  $k_a[RH]/k_d$  ratios. Again there is a parallel with polarity but little evidence for any important role of charge-transfer structures. In addition, hydrogen bonding may be important in the acetic acid solvent system.

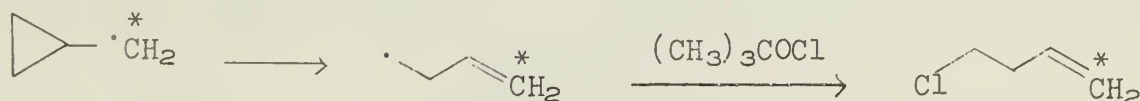
A much larger solvent effect upon  $k_a[RH]/k_d$  ratios has been observed for hypochlorite decompositions in the presence of olefins. For example, in the photolysis of benzyldimethylcarbinyl hypochlorite at 40° in as little as 3.6 mole % cyclohexene in cyclohexane, only cleavage products were observed.<sup>10</sup> Cyclohexane was not chlorinated and cyclohexene was recovered unchanged. Similar results were observed with a number of other hydrocarbons in the presence of small quantities of several different olefins. Here the effect appears to be of the charge-transfer variety rather than of polarity as was suggested for aromatic solvents. As mentioned previously, the



Halogenation of Substituted Toluenes, Cyclic Hydrocarbons, and Compounds with Polar Groups. Walling and Jacknow<sup>24</sup> carried out competitive chlorinations on a number of substituted toluenes with t-butyl hypochlorite at 40°. The relative reactivities yielded a linear Hammett plot with  $\rho = -0.83$ , implying that the t-butoxy radical is an electron-accepting species which preferentially attacks points of high electron availability. A better correlation with  $\sigma$ -values than  $\sigma^+$ -values for substituents was observed. This is consistent with the strongly exothermic, low activation energy process for hydrogen abstraction postulated previously.

The photochlorination of cyclopropane by Walling and Fredricks<sup>25</sup> yielded predominantly chlorocyclopropane with practically no ring-opened product. The chlorination of methylcyclopropane afforded cyclopropylcarbinyl chloride and ring-opened allylcarbinyl chloride as major products. The ring opening of the cyclopropylcarbinyl radical increased with temperature and was consistent with the process in scheme IV. The cyclopropylcarbinyl radical appears to maintain its classical structure

Scheme IV



because no scrambling of <sup>13</sup>C label was observed. The chlorination of 1,1-dimethylcyclopropane gave predominantly the chloromethyl derivative. The lack of attack upon the cyclopropane ring of the methyl- and 1,1-dimethylcyclopropanes is further supported by the recent observations of Freeman and co-workers.<sup>26</sup> They chlorinated bicyclo[3.1.0]hexane with t-butyl hypochlorite. Substitution occurred only at C-2 (78%) and C-3 (22%).

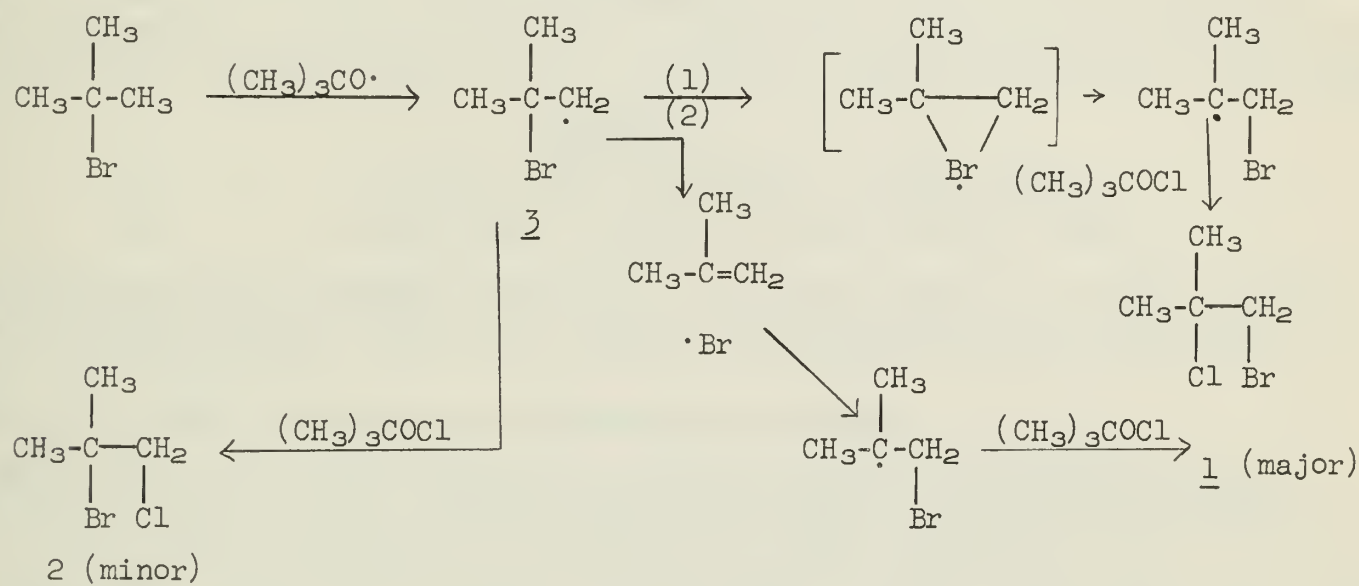
The hypochlorite chlorination of ethylene oxide yielded chloroethylene oxide (90-95%) with no detectable amount of ring cleavage product.<sup>25</sup> The chlorination of propylene oxide gave predominantly 2-chloropropylene oxide. Here in contrast to the methylcyclopropane case, attack occurred primarily on the 3-membered ring, presumably because of high electron availability at carbon adjacent to ether oxygen. Little ring opening occurred since only traces of chloroacetone were detected.

Skell, Allen, and Gilmour<sup>27</sup> chlorinated t-butyl bromide photochemically with t-butyl hypochlorite at -78°. The two products obtained were 1 and 2 shown in



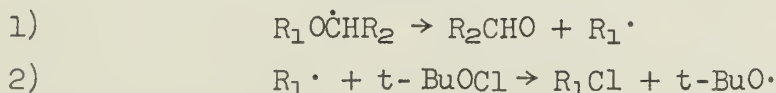
scheme V. The formation of rearranged product 1 was reduced at lower temperatures. The authors concluded that 1 was formed by hydrogen abstraction to give a bridged radical which then abstracted chlorine from the hypochlorite. Four years later Haag and Heiba<sup>28</sup> carried out the same reaction at  $-78^{\circ}$ . They observed an increase in 2 with increasing concentration of *t*-butyl hypochlorite. These results support the existence of the classical radical 3, which can be intercepted by chlorine from the hypochlorite to give 2. The proposed mechanism for the over-all reaction is illustrated in scheme V. Two routes are proposed for the formation of 1. Route (1) involves Skell's bridged radical. In route (2) the elimination of bromine from radical 3 is exothermic (est.  $\Delta H = -5$  kcal/mole) and should have a relatively low activation energy. Even at  $-78^{\circ}$  the elimination would be expected to be fairly fast. The scavenging of free bromine radicals by added allene with a corresponding reduction in product 1 lends support to route (2). Compound 1 appears to be formed, at least in part, by route (2).

Scheme V



The photochlorination of acyclic ethers with *t*-butyl hypochlorite yields alpha chloro ethers by the usual hydrogen abstraction scheme.<sup>29</sup> The relative reactivities for alpha hydrogen abstraction show the expected order primary < secondary < tertiary with considerable activation of alpha hydrogens compared with simple hydrocarbons. In contrast beta hydrogens are less reactive than those of comparable hydrocarbons. These results support the conclusion that *t*-butoxy radicals attack points of high electron availability. Competitive beta scission of the alpha-alkoxyalkyl radical gives rise to alkyl chlorides and carbonyl compounds as shown in scheme VI. In general, the ease of beta scission of the alpha-alkoxyalkyl radical parallels the

Scheme VI



stability of the radical eliminated as in the case of alkoxy radical decompositions. Interestingly, no cleavage of cyclic ethers was observed, except possibly for propylene oxide.

The reaction of both aromatic and aliphatic aldehydes with *t*-butyl hypochlorite to yield the corresponding acid chlorides occurs readily.<sup>29</sup> The chlorination of ketones in nonpolar solvents occurs by a radical chain process to yield alpha chloro ketones. In polar solvents, or in the presence of acid catalysts, the chlorination occurs by a polar mechanism.<sup>1</sup>

Spontaneous Initiation. A vigorous reaction of styrene with *t*-butyl hypochlorite in total darkness at  $0-5^{\circ}$  has been observed by Walling and co-workers.<sup>30</sup> The reaction was remarkable in that no irradiation or added radical initiator was necessary. The radical nature of the dark reaction was evidenced by its inhibition by radical



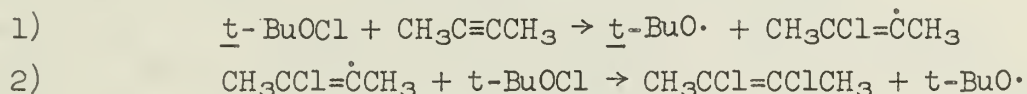


inhibitors, by the formation of the anti-Markovnikov product, 2-chloro-2-phenylethyl t-butyl ether, and by the induced chlorination of cyclohexane. Similar "spontaneous" reactions have been observed with substituted acetylenes.

The reaction of t-butyl hypochlorite with 2-butyne in the dark at room temperature yielded 1-chloro-2-butyne (major product), trans-2,3-dichloro-2-butene, and other products. Dark and light reactions gave practically the same yields. The quantitative yield of acetone and t-butyl alcohol indicated that essentially no addition to the acetylenic triple bond took place. Evidence for the radical reaction was seen in its inhibition by radical inhibitors and in the induced chlorination of added toluene.

Two possibilities for initiation of the radical chain can be eliminated. One involves the homolytic cleavage of t-butyl hypochlorite. This process is unlikely since similar dark reactions do not occur in the presence of other easily chlorinated substrates. The second involves initiation by adventitious impurities. This process appears unlikely because the high rates of reaction would require large amounts of initiator. The authors have suggested that initiation involves the concerted breaking of the O-Cl bond of the hypochlorite and addition of chlorine to the pi electron system of 2-butyne as shown in step (1) of scheme VII. The formation of small amounts of 2,3-dichloro-2-butene supports this "spontaneous" initiation process. The t-butoxy

#### Scheme VII



radicals produced then propagate the chain in the usual manner. At high concentrations, aldehydes and some ethers also undergo a spontaneous radical-generating process in the dark.<sup>29</sup>

#### KINETICS OF t-BUTYL HYPOCHLORITE CHLORINATION OF TOLUENE

Walling and Kurkov have studied the kinetics of the azobisisobutyronitrile-initiated reaction of t-butyl hypochlorite with toluene in carbon tetrachloride at 29.5° by following the hypochlorite disappearance spectrophotometrically.<sup>31,32</sup> In spite of careful purification of reagents and degassing, appreciable induction periods and sigmoid rate curves were observed. Consequently, kinetic measurements were taken in the maximum rate region. The rate of chain initiation was determined by the rate of disappearance of galvinoxyl in the presence of known concentrations of azobisisobutyronitrile. Under the reaction conditions beta scission was minor and was not considered to complicate the kinetics. The kinetic scheme involved initiation, propagation, and three possible bimolecular termination steps: (1) combination of two t-butoxy radicals, (2) two alkyl radicals, and (3) a t-butoxy radical with an alkyl radical. From steady-state approximations a solution for the system of equations of the kinetic scheme was obtained in the form of a quadratic equation. Graphical analysis of this quadratic equation provided rate constant ratios, which showed that termination via t-butoxy radical coupling is important below a toluene:hypochlorite ratio of 3 while cross-termination is important above a ratio of 3 and becomes negligible only at ratios less than one. The absolute rate constants for hydrogen abstraction from toluene ( $8.0 \times 10^4$  l./mole sec) and t-butoxy radical recombination ( $1.4 \times 10^9$  l./mole sec) were estimated by employing the concepts of diffusion-controlled reactions and cage processes.

Ingold and co-workers<sup>33a-c</sup> have studied the kinetics of the photochemically initiated reaction of t-butyl hypochlorite with toluene in carbon tetrachloride at 24°. The absolute rate constants for hydrogen abstraction from toluene ( $4.3 \times 10^3$  l./mole sec) and t-butoxy radical recombination ( $1.0 \times 10^8$  l./mole sec) were determined by the rotating sector method. In contrast to Walling's results, chain termination occurs chiefly by combination of t-butoxy radicals even at toluene:hypochlorite ratios greater than three. Although discrepancies exist between the results of Ingold and Walling, the general characteristics of the reaction are in agreement.

#### SUMMARY

The radical chain halogenation of a number of hydrocarbons and derivatives by



tertiary hypohalites has been examined. Beta scission of the alkoxy radical competes with the hydrogen abstraction process. The reactivity and selectivity of the t-butoxy radical is affected by aromatic, olefinic, and polar solvents. An unknown radical intermediate has been proposed to account for the discrepancies observed between direct and indirect measurements of the relative reactivity of aliphatic and benzylic C-H bonds. The halogenations of styrene and acetylenes involve spontaneous radical-generating processes. Hypohalites are fairly selective halogenating agents and provide a synthetically useful route for the halogenation of a variety of hydrocarbon derivatives. In addition, hypohalites are versatile substrates well suited for the study of the reactive properties of alkoxy radicals.

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THE DEOXYGENATION OF AROMATIC NITRO AND NITROSO COMPOUNDS  
BY TRIVALENT PHOSPHORUS DERIVATIVES

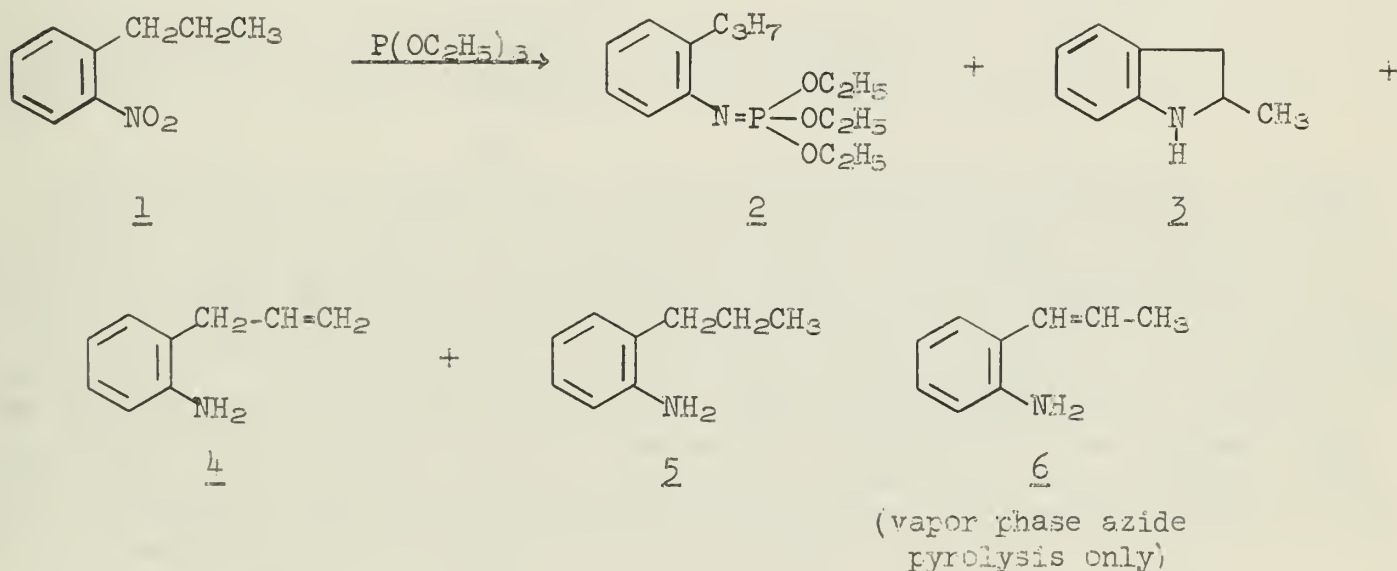
Reported by Herbert G. Seto

May 13, 1968

Recent investigations have established that reducing agents such as iron pentacarbonyl,<sup>1</sup> metal oxalates,<sup>2</sup> and trivalent phosphorus derivatives deoxygenate aromatic nitro and nitroso compounds. Depending on the reaction conditions and on the structure of the substrate, the products isolated have been azoxy compounds,<sup>3-5</sup> heterocyclic nitrogen compounds,<sup>3,5-7</sup> derivatives of phosphorimidic acid,<sup>3,7</sup> and tars.<sup>3,7</sup> Interest in these reactions stems from their synthetic value and from the controversy as to whether the mechanism involves nitrene or polar intermediates. This seminar will deal specifically with the mechanism involved in the thermal reaction<sup>8</sup> of trivalent phosphorus derivatives with aromatic nitro and nitroso compounds. The synthetic aspects of these reactions will also be briefly considered.

o-ALKYLNITRO- AND o-ALKYLNITROSOBENZENES

The thermal reaction of o-nitro- and o-nitrosoarenes with triethyl phosphite has been studied<sup>9</sup> to determine if the resulting deoxygenation produces nitrene intermediates. The criterion for nitrene intermediates was their reaction with adjacent saturated side chains to form C-H insertion products. o-Aliphatic- or o-alicyclic-nitrobenzene compounds when added in small portions to refluxing triethyl phosphite yielded products consisting of 46% of the corresponding triethyl N-arylphosphorimidates, 4% of the alkyl anilines, and, with the exception of the methyl derivative, 6.5-14% insertion and abstraction products. In particular, o-nitropropylbenzene (1) in refluxing triethyl phosphite gave 46% of the phosphorimide 2, 7% 2-methylindoline (3), 6% o-allylaniline (4), and 4% o-propylaniline (5). The unaccounted



material appeared as a residue which solidified to a brittle glass on attempted distillation. Trans-o-propylaniline (6), which was stable under reaction conditions was not observed in a VPC analysis of the reaction mixture. The amine reaction product, the phosphorimide, and the side products were believed to be consistent with a nitrene intermediate. Because aryl nitrenes are considered the precursors of the insertion products produced from pyrolysis of aromatic azides,<sup>10,11</sup> similarities of the deoxygenation and azide reactions would lend support to the formation of nitrene intermediates in the reactions of the nitro compounds. The deoxygenation<sup>12</sup> of (+)-(S)-2-nitro-1-(2-methylbutyl)benzene (7,  $R=NO_2$ ) yielded 25% of a partially active (ca. 50%) indoline 8. Solution phase photolysis of the azide (7,  $R=N_3$ ) yielded 60% of 8 with 65% optical purity.<sup>13</sup>

A comparison of the composition of the amine product mixture from the phosphite deoxygenation of o-nitropropylbenzene (1) and the product mixture from the vapor phase and solution (triethyl phosphate) pyrolysis of o-azidopropylbenzene appears in Table 1.



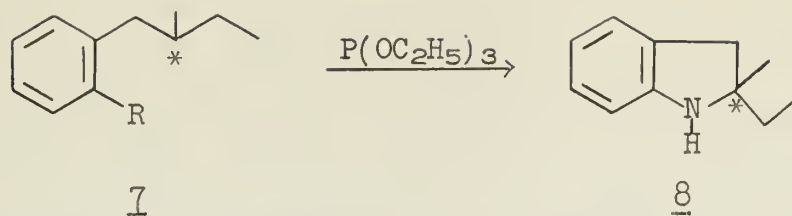
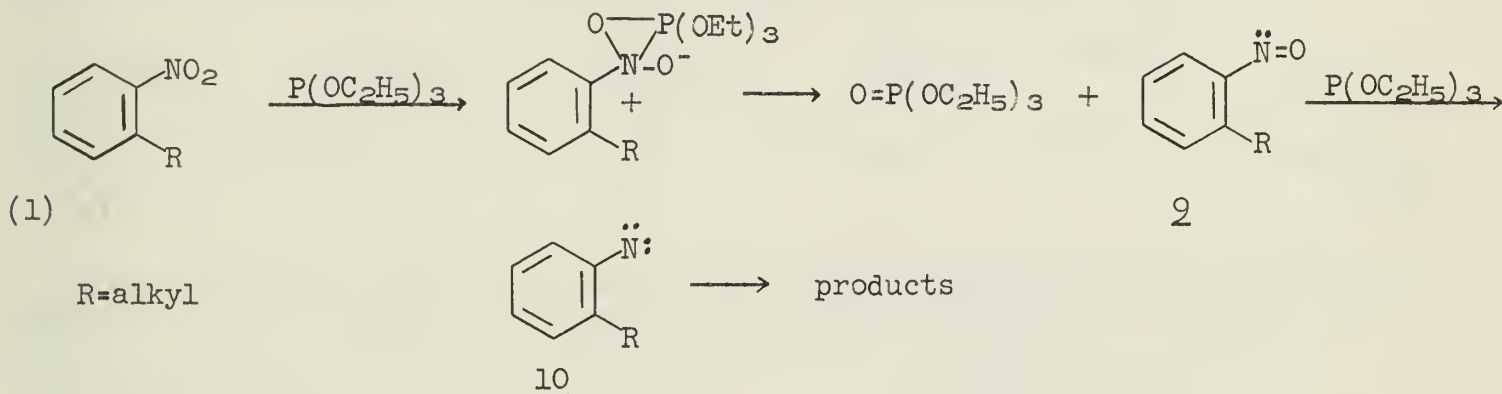


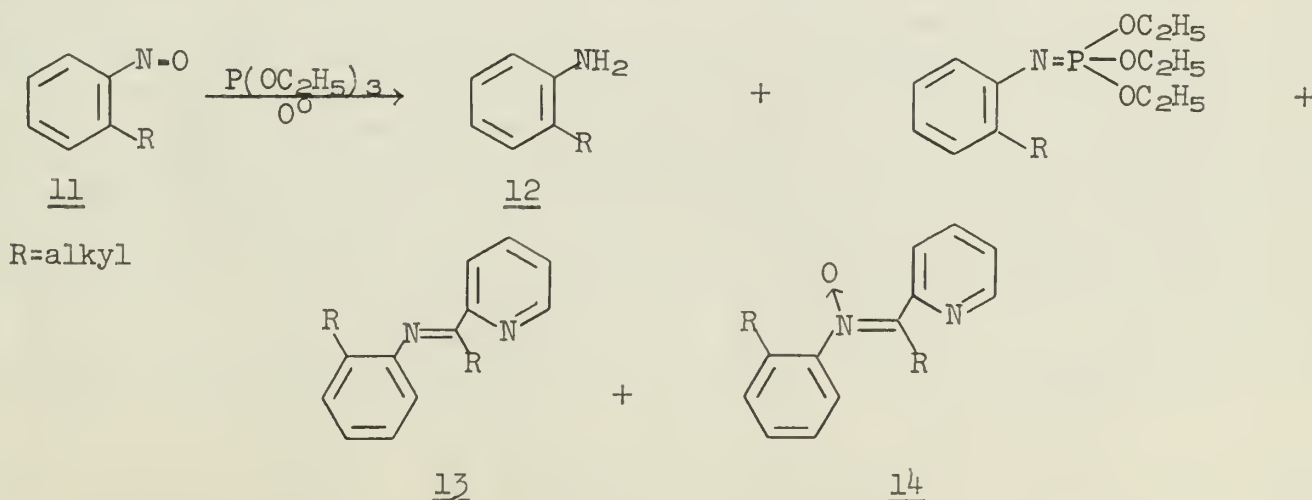
Table 1 Composition of Amine Mixtures

Compound	% total		
	deoxy- genation	azide soln.	photolysis vapor phase
<u>3</u>	43	38	51
<u>4</u>	39	34	34
<u>5</u>	18	28	trace
<u>6</u>	0	0	16

The general correlation of products from the azide and deoxygenation reactions lends support to an o-alkylimidobenzene intermediate 10, which in turn might be formed from an aryl nitroso precursor 9 as shown in eq (1).



If the nitro deoxygenation does proceed via the nitroso derivative, it might be expected that the products and their ratios from both types of substrate should be similar. Thus addition of the o-methyl-, propyl-, or butylnitrosobenzenes to refluxing triethyl phosphite (156°C) gave the corresponding phosphorimidate, alkylaniline, C-H insertion products, and abstraction products in yields of 6,6,1,>0.5% respectively. A brown tar constituted the unaccounted products. At 0°C the difference was that the only amines (insertion or addition products) formed were the o-alkylanilines. The reactions at each temperature produced two new compounds 13, (20%) and 14 (1%) with VPC retention times longer than the phosphorimidate. On the basis of product isolation and structure determination, the typical reaction of o-alkylnitrosobenzenes was thought to be as follows:



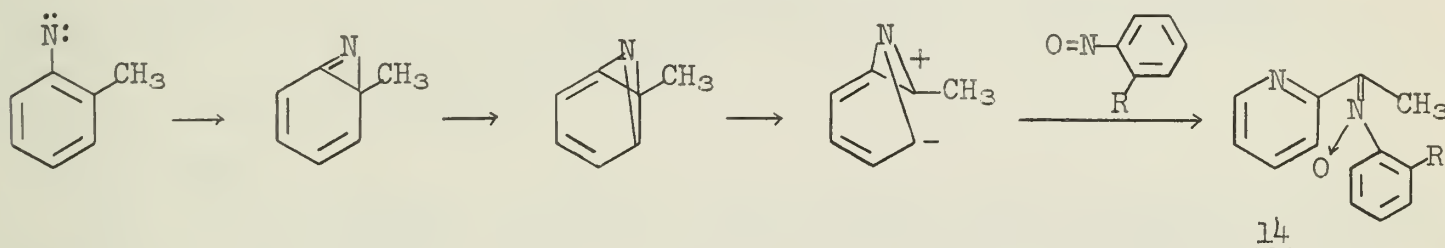
Compound 14 could be converted to 13 by treatment for one hour with triethyl phosphite. The fact that pyridine compounds were formed only with the nitroso



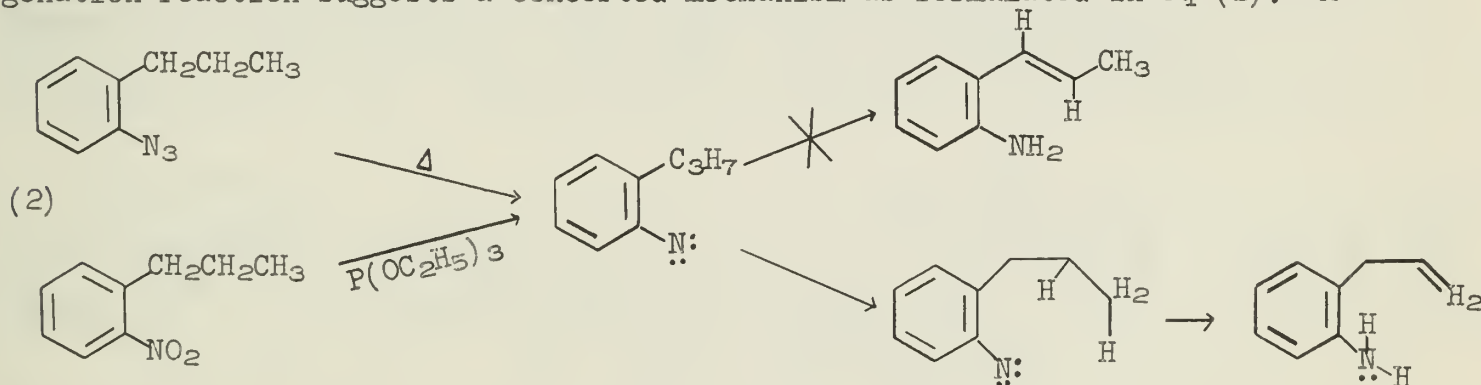


compounds does not rule out the possibility of nitroso intermediates in the corresponding nitro deoxygenation. Several hours of refluxing were required to completely deoxygenate the nitro compounds, but only a few minutes were required for complete reaction of the nitroso compounds, even at 0°C. The nitroso reaction was almost spontaneous at reflux temperatures of triethyl phosphite. The difference in nitro *vs* nitroso reactivity thus leads to differences in the nature of the reaction medium. Since the first oxygen transfer step must be slow compared to the second, the concentration of the nitroso intermediate is very small. The finite amount of nitroso compound after each addition leads to the possibility of a new mode of reaction for the deoxygenated intermediate, which results in an intramolecular reaction to give C-H insertion and hydrogen abstraction products. Other possible reactions are addition of the deoxygenated intermediate to triethyl phosphite to give the phosphorimide, or reaction with a nitroso molecule to give, after subsequent steps, 13 and 14. The decrease in amine and phosphorimide yields with nitroso as compared to nitro compounds suggests that the unreacted nitroso compound diverts some of the deoxygenated intermediate from the reaction path followed by the nitro compounds. The observed drop in concentration of 13 with a decrease in concentration of nitroso starting material is consistent with this suggestion.

The formation of 14 can be rationalized in terms of the 7-azabicyclo[4.1.0]-hepta-2,4,6-triene intermediate postulated by Huisgen and Appl<sup>14</sup> and by Doering and Odum<sup>15</sup> as a possible intermediate in the formation of 2-amino-3H-azepine derivatives from amines and thermally<sup>14</sup> or photolytically<sup>15</sup> generated phenylnitrenes.



The selective H-abstraction seen in the azido pyrolysis and the nitro deoxygenation reaction suggests a concerted mechanism as formulated in eq (2). A

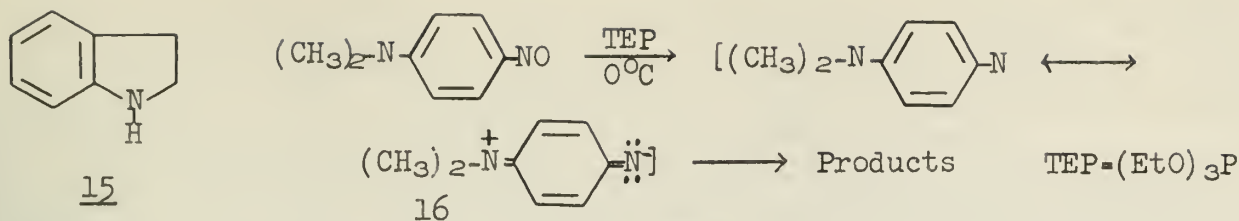


mechanism which invokes a discrete carbonium ion or radical at the  $\beta$ -carbon in the side chain is not likely, since none of the conjugated isomer was formed. Whether the formation of the conjugated isomer in the vapor phase pyrolysis of the azide results from thermal isomerization or a change in mechanism is still to be investigated.

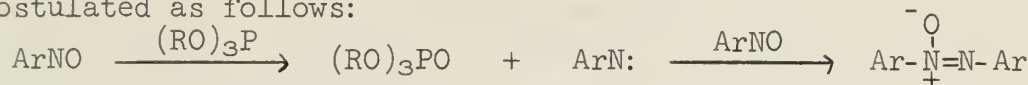
There are other similarities with azide pyrolyses besides the production of C-H insertion products, the selective formation of non-conjugated H-abstraction products, and a tendency to rearrange with the destruction of the original aromatic skeleton. For example, thermolysis<sup>16</sup> or photolysis<sup>15</sup> of phenyl azide yielded phenylnitrene which underwent ring expansion to a species that could be trapped by primary or secondary amines to give N-allyl derivatives of 2-amino-3H-azepines, which are also the type of products in the deoxygenation of nitrosobenzene by triethyl phosphine in the presence of primary and secondary amines.<sup>17,18</sup> The fact that only small yields of triethyl N-phenylphosphorimidates were isolated from the deoxygenation of nitrosobenzene<sup>3</sup> was attributed to very rapid ring expansion of the nitrene.

Bunyan and Cadogan<sup>3</sup> found that the reaction of *o*-ethylnitrosobenzene with triethyl phosphite yielded the corresponding azoxybenzene derivative. No dihydroindole (15) was isolated, although this product might be expected on the basis of reactions





of related azides.<sup>19</sup> The preferred reaction of the nitrene with unchanged nitroso compound is postulated as follows:



Stabilization of the nitrene intermediate by the introduction of a *p*-dimethylamino substituent<sup>20</sup> allows excess triethyl phosphite to compete with the nitroso compound for the electron deficient nitrogen atom, since the nitrene, if formed, should be stabilized as a result of contributions from 16.<sup>21</sup> Increasing the concentration of triethyl phosphite increased the yield of the phosphorimide and decreased the yield of azoxy compound. Analogous to the reaction of *p*-dimethylaminophenyl nitrene with triethyl phosphite is the reaction of carbenes with triphenylphosphine to give the corresponding methylene phosphoranes 17.<sup>22</sup> That no rearranged products were found

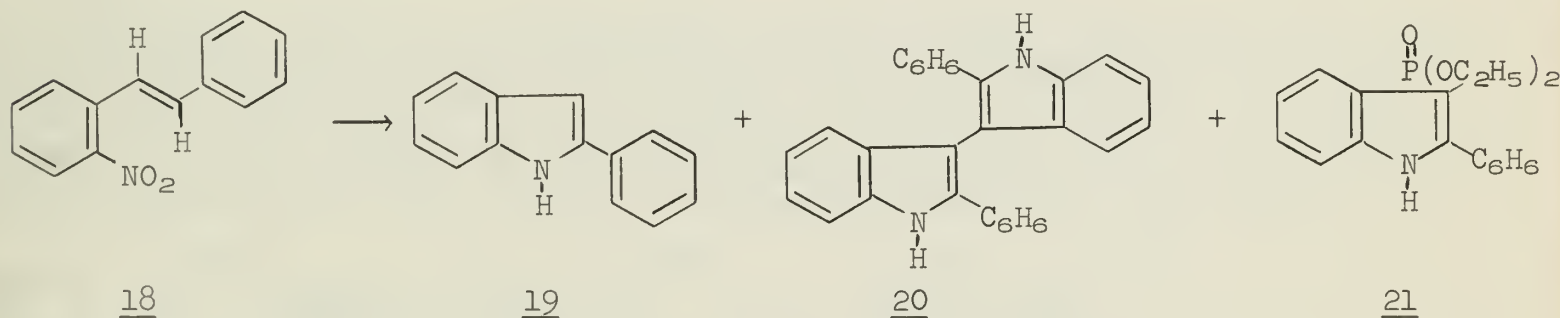


in the deoxygenation reaction of *o*-ethylnitrosobenzene by triethyl phosphite in benzene solution is in agreement with the known sensitivity of the phenyl nitrene rearrangement to the reaction medium.<sup>15,19</sup>

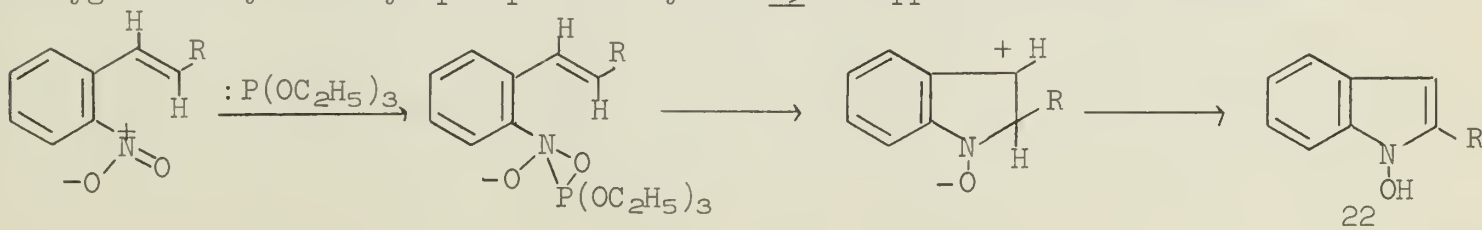
## REDUCTIVE CYCLIZATION REACTIONS

### A. NITROSTYRENES

When triethyl phosphite was used to reduce aromatic nitro compounds containing an adjacent unsaturated side chain, the main product formed was a heterocyclic nitrogen compound.<sup>6,23</sup> Sundberg<sup>7</sup> has reacted several  $\beta$ -substituted *o*-nitrostyrenes with refluxing triethyl phosphite to obtain 2-substituted indoles. From the reaction of *trans*-*o*-nitrostilbene (18) with the alkyl phosphite were produced 71% 2-phenylindole (19), 7% 2,2'-diphenyl-3,3'-bi-indole (20), and 1.6% diethyl 2-phenyl-3-indolylphosphonate (21). Several mechanistic pathways have been proposed for the



reductive cyclization of *o*-nitrostyrenes. Bunyan and Cadogan<sup>3</sup> have isolated heterocyclic ring compounds from the reaction of nitroso compounds with triethyl phosphite. Nitrene intermediates were postulated.<sup>3,24</sup> Sundberg<sup>25</sup> proposed that whether a nitrene or nitroso intermediate was involved, ring closure occurred before total deoxygenation of the nitro atom and that the new C-N bond formed concurrently with or immediately after the first deoxygenation step to yield a 1-hydroxyindole 22, which was further deoxygenated by triethyl phosphite to yield 19. Support for this mechanism came from



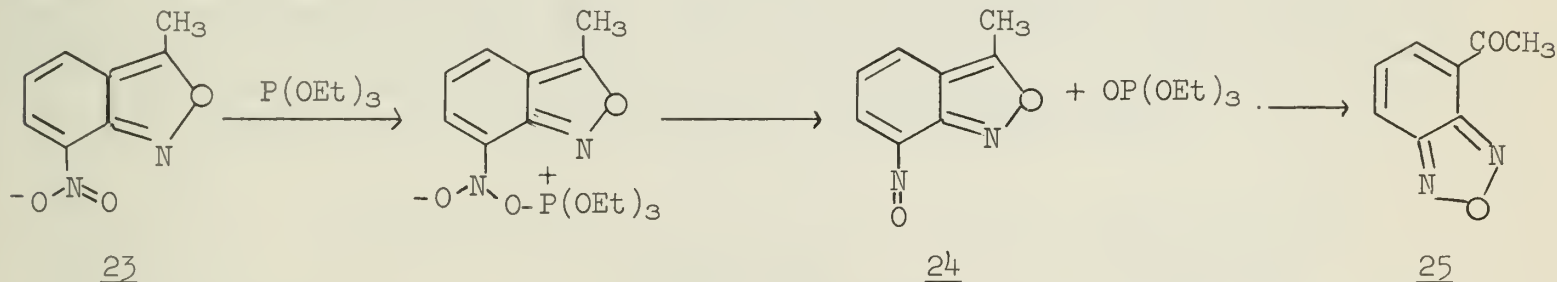




the fact that the product ratios for deoxygenation of 1-hydroxy-2-phenylindole (22,  $R=C_6H_5$ ) were quite close to that of the corresponding styrene, the ratio of 19 to 20 being somewhat higher with the indole starting material because no triethyl phosphite was used for a first deoxygenation step. Samples taken after one hour from reactions involving the trans-o-nitrostilbene gave a 15% yield of 22.

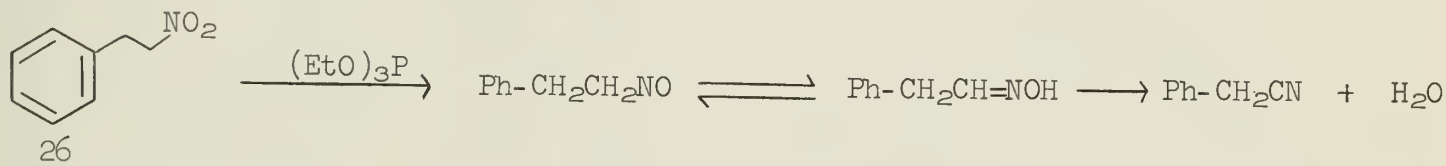
The source of the dimer 20 is postulated to be 22, but the mechanistic path is uncertain. The yield of 20 increased with decreasing alkyl phosphite concentration, since there was less phosphite to deoxygenate the hydroxyindole. Catalysis of 22 to 20 by some component in the reaction mixture was also probable since 22 could be cleanly converted to 20 by refluxing in *p*-cymene, but could not be converted by refluxing in pure triethyl phosphite.

Further evidence of reduction through a nitroso intermediate has been presented by Katritzky and co-workers.<sup>28a</sup> A 60% yield of 4-acetylbenzofurazan (25) was obtained by the triethyl phosphite reduction of 3-methyl-7-nitroanthranil (23). Katritzky had

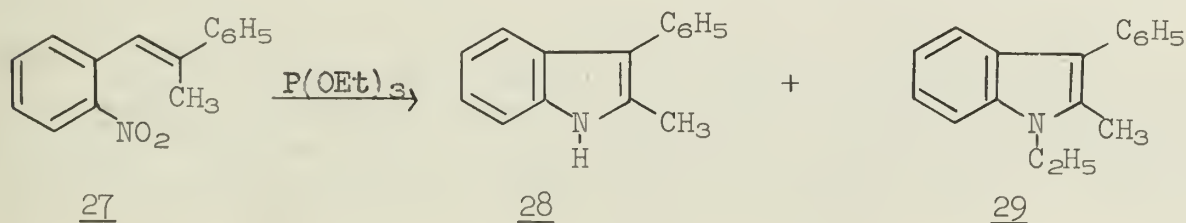


previously shown that nitrosation of 5-dimethylaminobenzofuroxan gave 4-dimethylamino-7-nitrobenzofurazan. Thus, since tertiary aromatic amines could be C-nitrosated, it seems reasonable that compounds of type 24 can rearrange to 25.

When 1-nitro-2-phenylethane (26) was allowed to react with triethyl phosphite, phenylacetone nitrile was formed, presumably via the oxime since the nitrile could also be obtained by starting with the oxime.<sup>12</sup> These results also suggest the possibility of a nitroso intermediate.



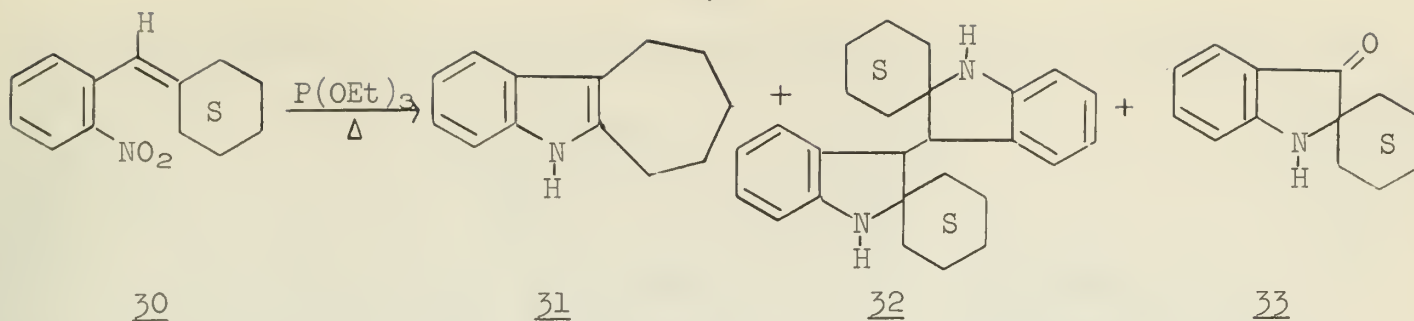
Studies of  $\beta,\beta$ -disubstituted *o*-nitrostyrenes<sup>25</sup> indicate that cyclization occurs by electrophilic attack at the double bond followed or accompanied by a 1,2-shift of a substituent from the 2-carbon of the indole ring system to produce a rearranged indole as the main product.  $\beta$ -Methyl- $\beta$ -phenyl-*o*-nitrostyrene (27) when refluxed with triethyl phosphite yielded 77% 2-methyl-3-phenylindole (28) and 21% 1-ethyl-2-methyl-3-phenylindole (29). In an attempt to distinguish between the nitrene and N-



hydroxyindole mechanisms, the deoxygenation of 27 was interrupted several times to isolate 1-hydroxy-2-phenylindole; however, none was found in this case. Distinction between the two mechanisms is still not possible since the rate of deoxygenation of some hydroxyindoles may be such that no detectable concentration can form.

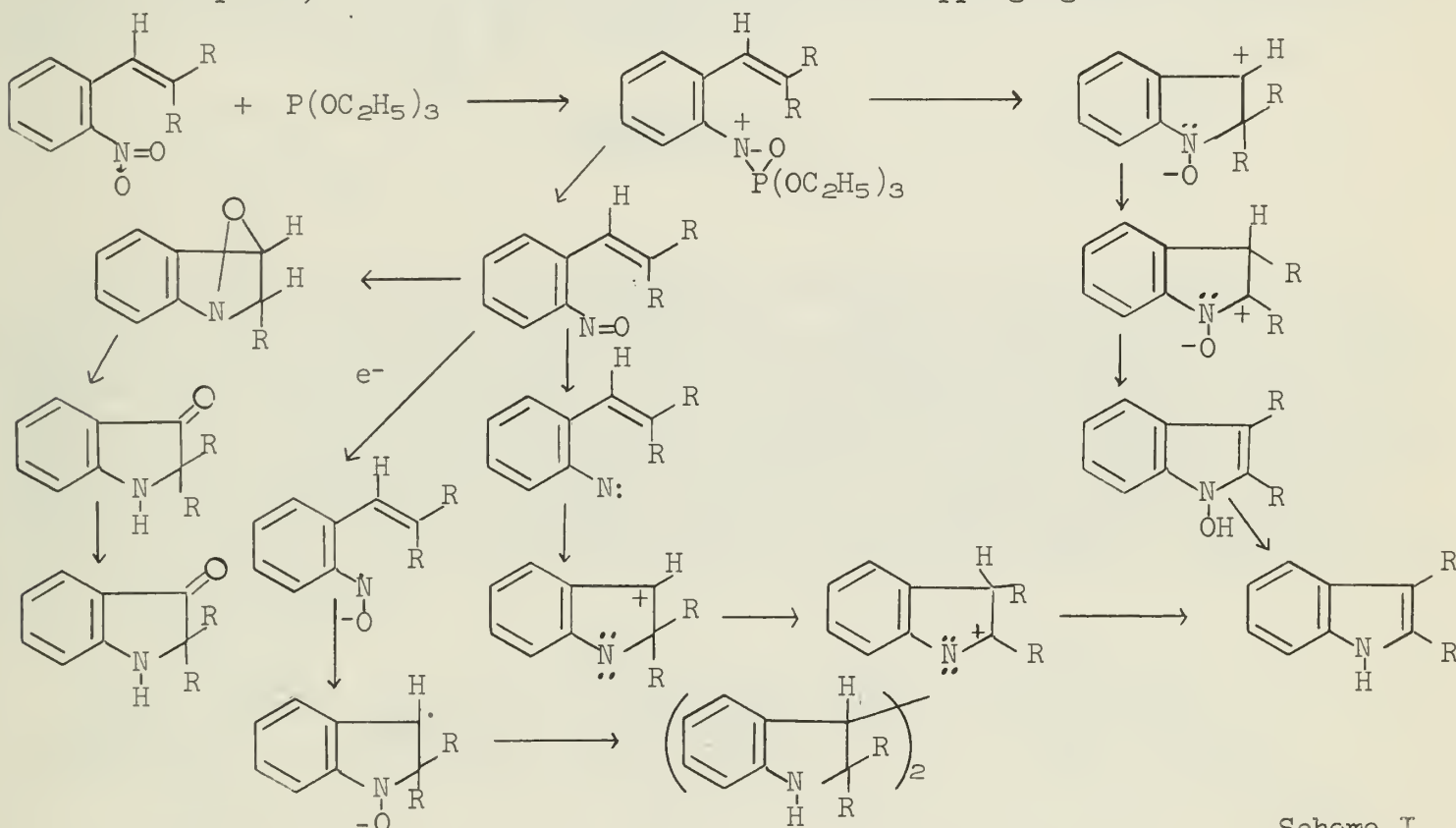
In the  $\beta,\beta$ -disubstituted *o*-nitrostyrenes, the phenyl is a much more effective migrating group than the alkyl group, a fact pointed out by yields two times greater for phenyl than alkyl adducts. Thus, when cyclohexylidene(*o*-nitrophenyl)methane (30) was treated with triethyl phosphite, only a 35% yield of 5,6,7,8,9,10-hexahydrocyclohept[b]indole (31) was realized. Two other products, 24% of the dimeric indoline, 3'-3'''-bispiro[cyclohexane-1,2'-indoline] (32), and 8% spiro[cyclohexane-1,2'-indolin-3'-one] (33) were also isolated. Apparently poor migrating groups allow competition by





reaction paths other than those which involve a 1,2-rearrangement. For example, aromatic nitroso compounds can act as electron acceptors to give radical anions.<sup>27</sup> Thus, in competition with an ionic reaction may be a free radical reaction, which would lead to the dimer. The N-hydroxyindole intermediates could act in the capacity of electron donors. The dimeric indoline could also possibly result from an ionic sequence of reactions initiated by alkylation of unreacted *o*-nitrostyrene by the cyclized, but unrearranged, carbonium ions. The various reaction paths are summarized in Scheme I.

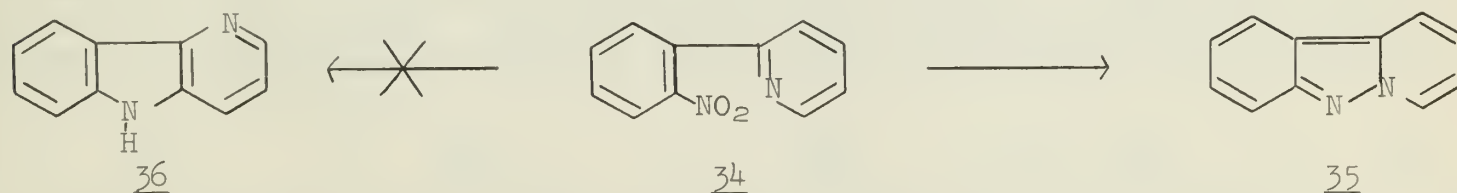
No reactions have been reported in which an unsaturated molecule, unattached to the nitro compound, was used as an external nitrene trapping agent.



Scheme I

#### B. NITROBIARYLS AND RELATED COMPOUNDS - SOME SYNTHETIC ASPECTS

Several workers have found<sup>3,6,28</sup> that 2-*o*-nitrophenylpyridine (34) when reacted with refluxing triethyl phosphite cyclized exclusively at the relatively electron-rich pyridine nitrogen atom to give a >90% yield of pyrido[1,2-*b*]indazole (35) rather than the alternative product of ring closure,  $\delta$ -carboline (36). Because ring closure occurs

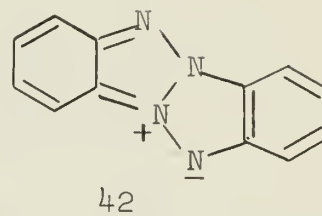
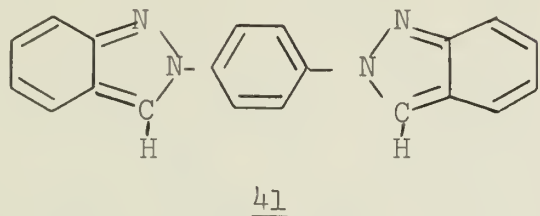
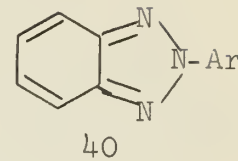
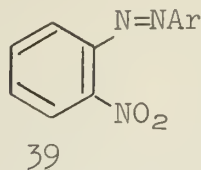
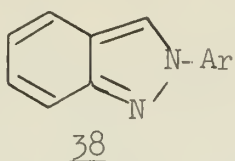
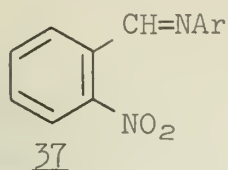


at nitrogen with the formation of a conjugated product, a convenient route to indazoles and triazoles is available. Thus *o*-nitroanils<sup>6,29</sup> 37 (Ar=Ph, *p*-C<sub>6</sub>H<sub>4</sub>CH<sub>3</sub>, *o*-C<sub>6</sub>H<sub>4</sub>Br,  $\alpha$ -C<sub>10</sub>H<sub>7</sub>) are readily converted into the corresponding indazole 38 with refluxing triethyl phosphite. Similarly, 2-nitroazobenzenes 39 (Ar=Ph, *p*-C<sub>6</sub>H<sub>4</sub>OCH<sub>3</sub>, *p*-C<sub>6</sub>H<sub>4</sub>Cl) are deoxygenated to the corresponding benzotriazoles 40 (50-70%), while bis-



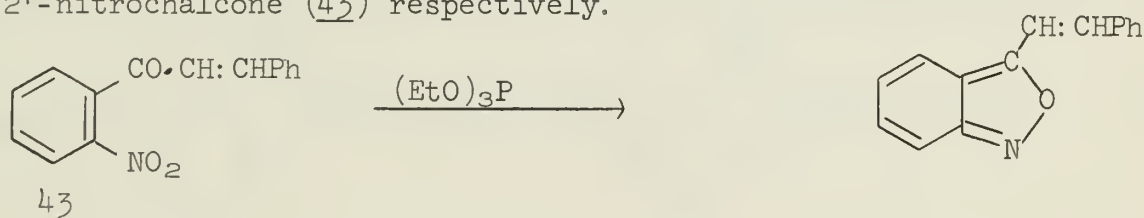


(*o*-nitrobenzylidene)-*p*-phenylenediamine yields *p*-di-2*H*-indazol-2-ylbenzene (41).

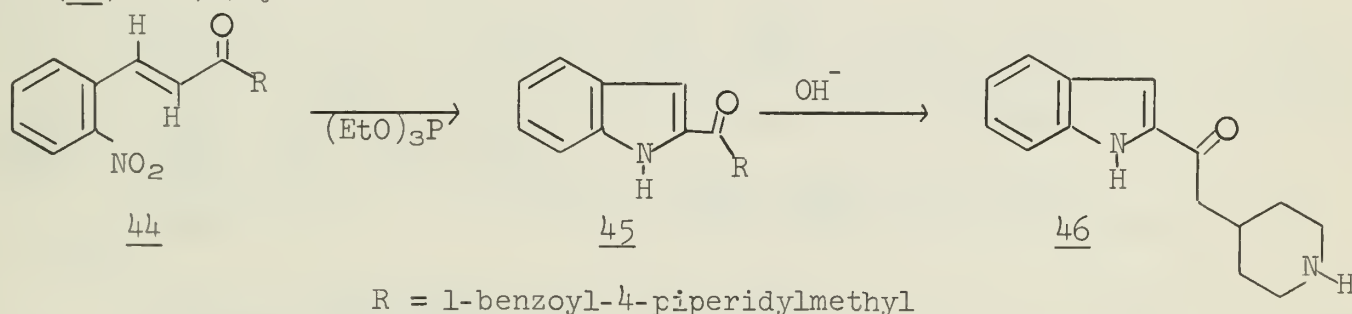


Polycyclic compounds containing fused five-membered rings can be synthesized in moderate yields. For example, reduction of 2,2'-dinitroazobenzene yields 63% of dibenzo[b,f]-1,3a,4,6a-tetra-azapentalene (42).<sup>6</sup>

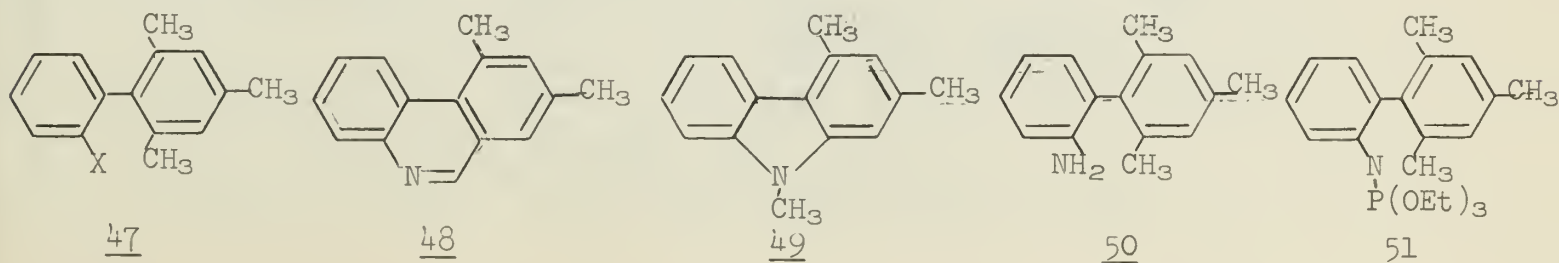
The phenothiazine and anthranil ring systems may be conveniently produced<sup>23</sup> in 54% yields by triethyl phosphite reduction of, for instance, 2-nitrophenyl phenyl sulfide and 2'-nitrochalcone (43) respectively.



An attractive use of nitro deoxygenation reactions is for the synthesis of 2-acylindoles from  $\beta$ -substituted *o*-nitrostyrenes. Impetus for investigation of this synthesis has been the report that a number of alkaloids containing the 2-acylindole structural unit have been isolated.<sup>30</sup> Use of 2-acylindoles as precursors for the synthesis of the dimeric indole alkaloids, demonstrated by Buchi and co-workers in their synthesis of voacamine,<sup>31</sup> prompted Sundberg<sup>32</sup> to try the reductive cyclization reaction in the synthesis of structures related to the vobasine family. Reflux of nitrostyrene 44 with triethyl phosphite produced 2-acylindole (45) in 13% yield. Alkaline hydrolysis of the benzoyl group gave the desired 2-indolyl 4-piperidylmethyl ketone (46) in 78% yield.



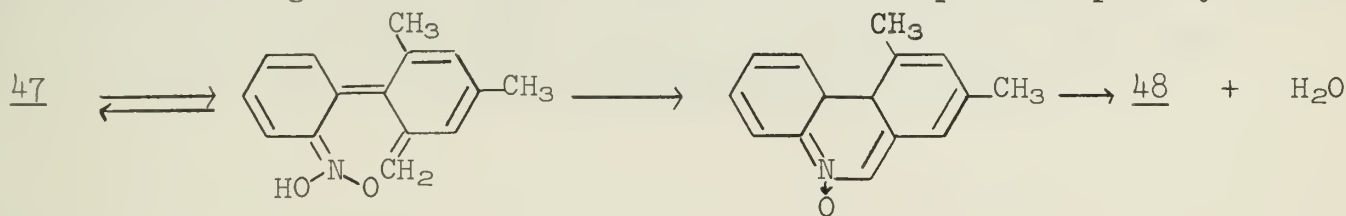
A mechanistic path for the 2-nitrobiaryl reactions has not been established. Similarity in behavior of simple 2-nitrobiaryls and 2-*o*-2-nitrophenylpyridine with their corresponding azides suggests nitrene intermediates. For instance, the thermal decomposition of 2'-azido-2,4,6-trimethylbiphenyl 47 (X=N<sub>3</sub>) in hexadecane yielded products 48, 49, and 50.<sup>19a</sup> Reduction of the nitro compound 47 (X=NO<sub>2</sub>) with triethyl phosphite<sup>18</sup> and triphenyl phosphine,<sup>6</sup> both of similar reactivity at 130°C, produced 13% of 50 and 15% of 51.





Since phosphorus trichloride,<sup>6</sup> a weaker nucleophile, was unable to reduce the 2-substituted biphenyl at 130°, nucleophilic attack by trivalent phosphorus on the nitro oxygen seems reasonable. As suggested above, the nitroso compound is perhaps an intermediate in the deoxygenation of the nitro group. Abstraction of the oxygen on the nitroso group could produce a nitrene intermediate which would abstract hydrogen and couple with the excess triethyl phosphite rather than undergo the presumably energetically less favorable insertions. When the nitro compound was allowed to react with triethyl phosphite in a 50 mole excess of (A) isopropylbenzene and (B) t-butylbenzene, 48 was formed in 14% yield along with 50 and 51.<sup>18</sup> The amount of hydrogen abstraction increased in solvent A [50; 32% vs 19% in (B)] with the concomitant formation of bi- $\alpha$ -cumyl (11%). Apparently there was abstraction by a triplet species to give an  $\alpha$ -cumyl radical which dimerized.

Maintaining a diphenyl ether solution of 47 (X=NO<sub>2</sub>) at 350°C for several hours results in a 32% yield of 48.<sup>13</sup> In this case, product formation can be attributed to cyclization of an *aci*-tautomer. A similar reaction mechanism<sup>33,34</sup> has been postulated for phenazine formation from 2-nitrodiphenylamine in the presence of ferrous oxalate. An immediate difficulty arises from this mechanism when no *aci*-nitro structure can be written, as is the case for the unsubstituted 2-nitrobiphenyls. In such cases mechanisms involving nitrene intermediates are the most probable pathways.



## CONCLUSION

Aromatic nitro compounds containing a saturated or unsaturated *ortho* substituent yield phosphorimidates or nitrogen containing heterocycles respectively upon treatment with trivalent phosphorus species. Although a mechanism involving nitrene intermediates seems likely, mechanisms involving nitroso and N-hydroxyindole intermediates have not been eliminated. Nitro biaryls offer a convenient synthetic route to indazoles, triazoles, and anthranils.

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## THE SYSTHESIS AND CHEMISTRY OF 7,7-DICYANONORCARADIENES

Reported by James H. Klug

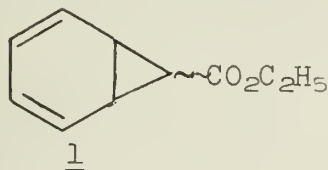
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## INTRODUCTION

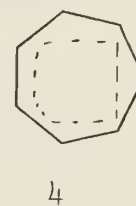
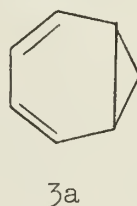
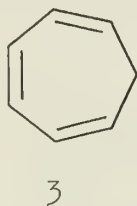
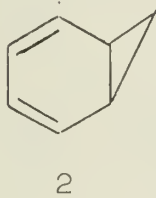
This seminar will deal with the syntheses and reactions of the 7,7-dicyanonorcaradienes. A brief description of norcaradiene-cycloheptatriene ring systems as well as recent reports concerning syntheses of stable norcaradienes will also be presented.

## NORCARADIENE AND CYCLOHEPTATRIENE RING SYSTEMS

Ever since the appearance of a paper by Büchner and Curtius in 1885 describing the supposed systhesis of ethyl bicyclo[4.1.0]hepta-2,4-diene carboxylate (1) as one of the products formed in the thermal decomposition of ethyl diazoacetate in benzene,<sup>1-3,9</sup> the existence of stable norcaradiene systems has been a subject of research for many investigators. Several excellent articles and reviews have appeared describing norcaradiene-cycloheptatriene ring systems.<sup>4-7</sup>

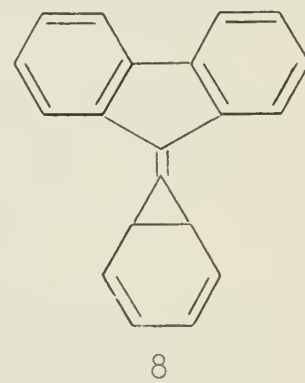
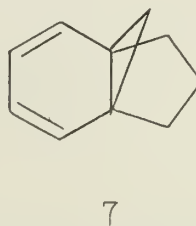
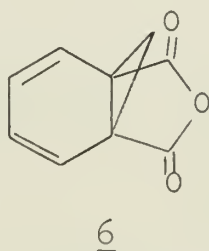
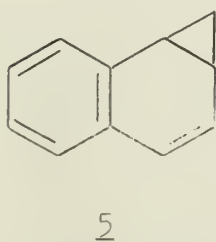


The relationship between norcaradiene and cycloheptatriene ring systems can be examined by considering three basic limiting cases.<sup>5</sup> Both cycloheptatriene and



norcaradiene can be pictured as being separate and distinct molecules with no inter-conversion occurring between the two due to the existence of a high energy barrier separating the systems. In the second limiting case, 2 and 3 can be considered to exist in a rapid valence-tautomer equilibrium as in the bicyclo[4.2.0]octa-2,4-diene/1,3,5-cyclooctatriene system.<sup>8</sup> Finally, norcaradiene can be pictured as a pseudoaromatic, planar molecule 4 with a formal 1,6 bond.<sup>9</sup> In this homobenzene formulation<sup>10</sup> 3 and 3a are then resonance hybrids of 4. Each of these three interpretations has been expanded to include many systems capable of existing in either a norcaradiene or cycloheptatriene form and the validity of these interpretations supported or criticized by several investigators. For a thorough discussion of these different points of view the reader is referred to Maier's excellent review.<sup>5</sup>

Up until 1965 the existence of a simple, stable norcaradiene had yet to be shown. However, examples of constrained norcaradiene ring systems were not lacking.

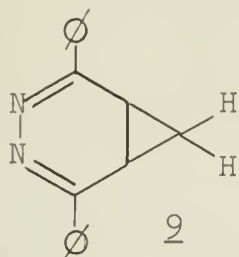


2,3-Benzonorcaradiene (5) is stabilized by incorporation of one of the double bonds into an aromatic system.<sup>11,12</sup> Formation of three-membered bridges across the 1,6 bond in 6 and 7 prohibit a cycloheptatriene structure because of concomitant formation of bridgehead double bonds.<sup>13</sup> Also, isomerization of the stable, substituted methylene norcaradiene (8) to its monocyclic tautomer would result in the formation of a





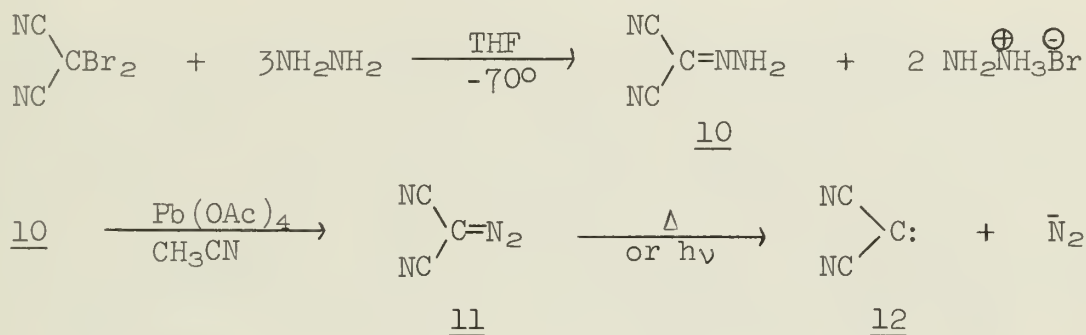
sterically hindered molecule.<sup>14</sup> Maier,<sup>15</sup> in 1962, demonstrated that norcaradienes can be stabilized by incorporation of a pair of nitrogen atoms into the ring at positions three and four.



It was found that 2,5-diphenyl-3,4-diazanorcaradiene (9) and its substitution products were stable at room temperature. However, it was not known whether this stabilization was due to the nitrogen atoms or merely to the conjugative effect of the phenyl groups.<sup>16</sup>

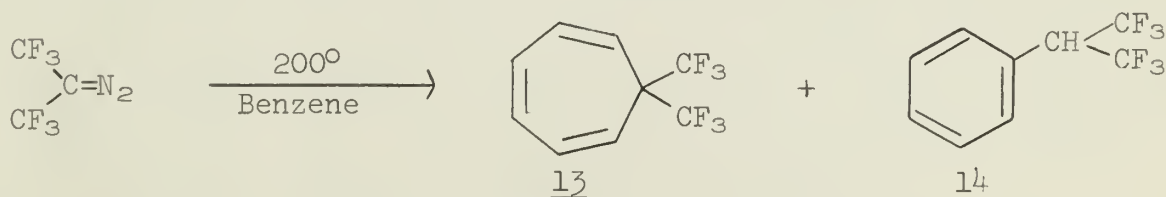
#### PREPARATION AND STRUCTURAL PROOFS OF 7,7-DICYANONORCARADIENES

Early in 1965 Ciganek<sup>17-19</sup> reported the preparation of dicyanodiazomethane. Reaction of dibromomalononitrile with hydrazine in tetrahydrofuran at  $-70^{\circ}$  gave carbonyl cyanide hydrazone (10) in yields of up to 40%. Subsequent oxidation of 10 with lead tetraacetate in acetonitrile afforded dicyanodiazomethane (11) in practically quantitative yield. Dicyanodiazomethane, although quite stable in moderately high acid concentrations, loses nitrogen readily on heating to  $70^{\circ}$  or on irradiation with ultraviolet light to yield dicyanocarbene (12). The resulting dicyanocarbene

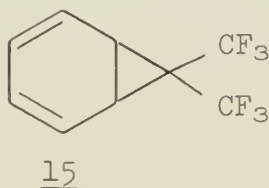


is so reactive that Ciganek<sup>18</sup> could find no solvent that did not react with it. The ground state of dicyanocarbene was proposed to be a triplet as expected on the basis of Skell's rationalizations.<sup>18,20</sup> This conclusion was also supported by evidence from studies on the esr spectrum of photolytically generated dicyanocarbene at low temperatures.<sup>21</sup> The above conclusion assumed spin conversion in the thermolytic formation of 12 from dicyanodiazomethane and was also based upon the notion that singlet carbenes add stereospecifically to double bonds and triplet carbenes non-stereospecifically.<sup>22</sup>

Gale<sup>24</sup> and coworkers, in 1966, had found that the pyrolysis at  $200^{\circ}$  of bis(trifluoromethyl)diazomethane, prepared by the lead tetraacetate oxidation of the corresponding hydrazone in benzonitrile at  $0^{\circ}$ , in excess benzene gave a 70% yield of 7,7-bis(trifluoromethyl)-1,3,5-cycloheptatriene (13) (88%) and hexafluoroisopropylbenzene (14) (12%). The tropilidene structure of 13 was established over that of the



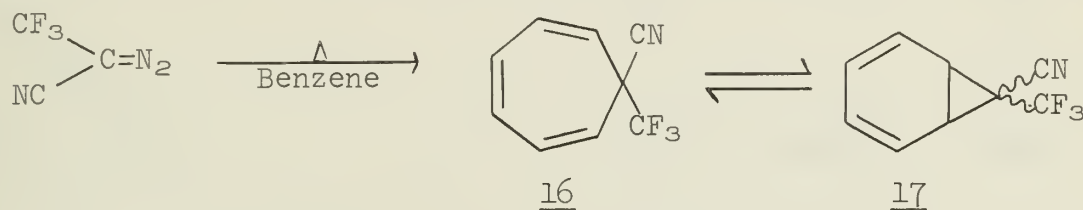
norcaradiene structure (15) on the basis of nmr data. A sharp singlet at  $\tau 5.58$  was observed in the  $\text{F}^{19}$  nmr spectrum of the main reaction product and this singlet remained unchanged in the temperature range of  $-120$  to  $+140^{\circ}$ . 7,7-Bis(trifluoromethyl)norcaradiene (15) would be expected to have nonequivalent trifluoromethyl groups and the absence of two signals in the  $\text{F}^{19}$  nmr spectrum therefore pre-





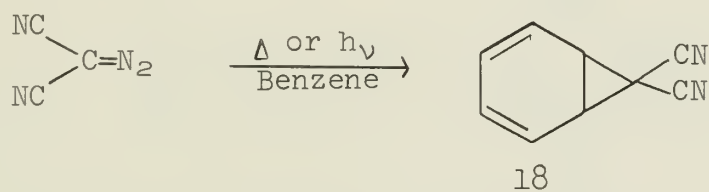
cluded its existence as an observed reaction product. In addition to the  $F^{19}$  nmr spectrum, the pmr spectrum of 13 had a four proton multiplet at  $\tau$ 3.6 and a two proton multiplet at  $\tau$ 4.6. 7,7-Bis(trifluoromethyl)norcaradiene would be expected to have a two proton absorption at a much higher field due to the presence of a cyclopropane structure. As a final structural proof, catalytic hydrogenation of 13 on a palladium-charcoal catalyst proceeded with the uptake of three molar equivalents of hydrogen and gave exclusively 1,1-bis(trifluoromethyl)cycloheptane. Photolysis of bis(trifluoromethyl)diazomethane in benzene also gave the same reaction products.

However, thermolysis of cyanotrifluoromethyldiazomethane in benzene at room temperature was reported by Ciganek<sup>36</sup> to give a 77% yield of a rapidly equilibrating mixture of 7-cyano-7-trifluoromethylcycloheptatriene (16) and 7-cyano-7-trifluoromethylnorcaradiene (17) with 16 predominating. The low temperature ( $-112^\circ$ ) nmr



spectrum of the mixture showed, besides the olefinic absorption, a broad singlet at  $\tau$ 7.05 assigned to protons 1 and 6 in 17. The  $F^{19}$  nmr spectrum of the mixture at  $25^\circ$  showed only a singlet at +4125 cps relative to fluorotrichloromethane. The low temperature  $F^{19}$  nmr spectrum, however, showed a singlet at +4187 cps and another singlet at +3760 cps with the high field singlet assigned to the trifluoromethyl group of 16 and the low field singlet assigned to the trifluoromethyl group of 17. The absence of a third signal in the low temperature  $F^{19}$  nmr spectrum indicated that only one of the two possible isomers of 17 was present in detectable amounts.<sup>36</sup>

In 1965 Ciganek<sup>19,23</sup> reported that the thermolysis or photolysis of dicyanodiazomethane in benzene gave an 82% yield of 7,7-dicyanonorcaradiene (18). The structural



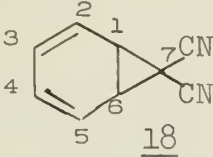

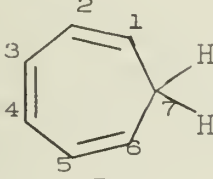
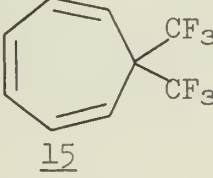
assignment was supported by ultraviolet spectral data which showed  $\lambda_{max}$  at 271 m $\mu$  ( $\lambda_{max}$  for 7-cyanocycloheptatriene is at 255 m $\mu$ ).<sup>25</sup> The Raman spectrum of 18 showed the double bond stretching band at 1568  $cm^{-1}$  with a relative intensity of 76 (taking the cyano band at 2248  $cm^{-1}$  as 100). In 7-cyanocycloheptatriene the corresponding band occurs at 1530  $cm^{-1}$  with an intensity of 610 (relative to the cyano band at 2245  $cm^{-1}$ ). The nmr spectrum ( $CDCl_3$ ) of 18 showed a four proton multiplet at  $\tau$ 6.53. The  $\tau$ 6.53 absorption, which is rather low for cyclopropane protons, is most likely due to the contribution of the magnetic anisotropy of the cyano group above the six member ring.<sup>18,26</sup> Roberts<sup>26</sup> has recently examined the high resolution 100 Mc proton spectrum of 18 which is classified as an AA'BB'XX' system. It was found that double irradiation of the 1,6 protons afforded an AA'BB' system very similar to that of naphthalene. The results of a computer analysis<sup>27-29</sup> of the AA'BB'XX' system afforded coupling constants which are listed in Table 1 along with comparable data reported for the cycloheptatriene and bis(trifluoromethyl)cycloheptatriene systems.<sup>30</sup>

The thermolysis of dicyanodiazomethane in p-xylene<sup>23</sup> afforded 2,5-dimethyl-7,7-dicyanonorcaradiene (19) and 1,4-dimethyl-7,7-dicyanonorcaradiene (20) in 41 and 39% yields, respectively. The crude products were purified by chromatography on alumina and separated by repeated fractional crystallization from cyclohexane. The nmr spectrum of 20 showed one methyl group as a singlet at  $\tau$ 8.27 and the other as a doublet ( $J = 1$  cps) at  $\tau$ 7.97. The sole cyclopropyl proton appeared as a doublet ( $J = 6$  cps) at  $\tau$ 6.88 and the three olefinic protons appeared as a distorted AB quartet centered at  $\tau$ 3.80. The nmr spectrum of 19 was remarkably simple consisting of three singlets at  $\tau$ 3.81 (2H), 6.78 (2H), and 7.87 (6H). In addition to spectroscopic

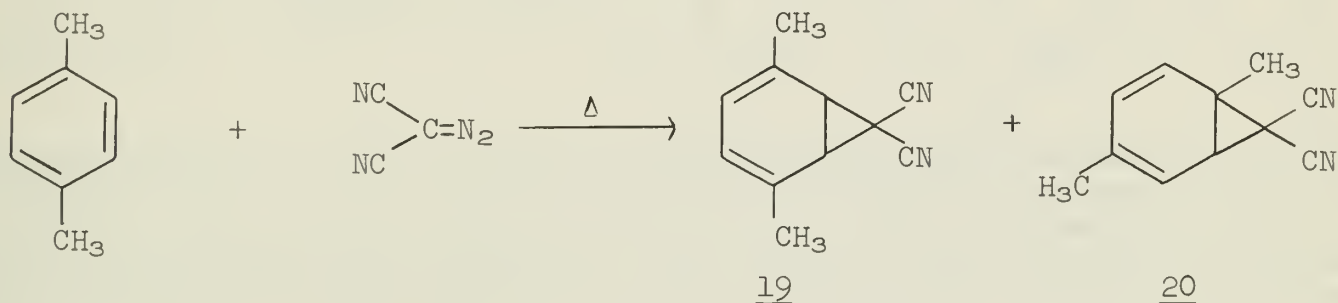




Table 1  
Comparison of Coupling Constants (in cps) of 18, 15, 3, and 1,3-Cyclohexadiene<sup>a</sup>.

	$J_{1,6}$	$J_{2,3}$	$J_{2,4}$	$J_{2,5}$	$J_{3,4}$
 <u>18</u>	8.4	9.38	0.84	1.12	6.22
 <u>3</u>	--	9.42	1.06	0.91	5.41
 <u>15</u>	--	5.26	0.80	0.00	10.67
 <u>15</u>	--	6.86	0.80	0.10	10.37

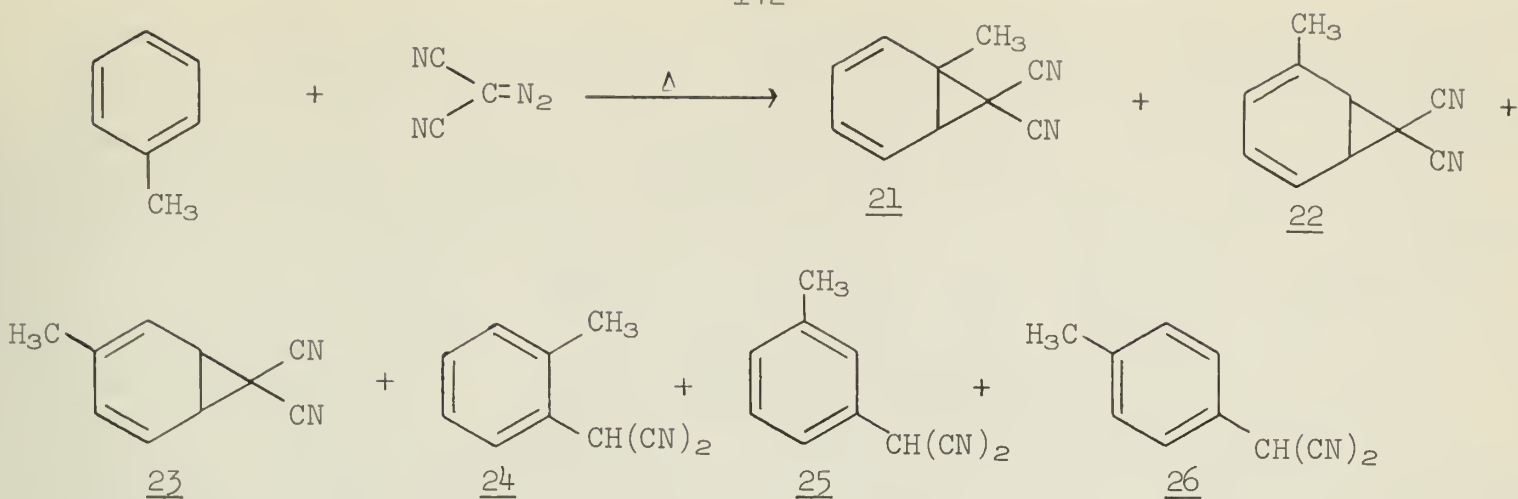
a. decoupled spectra



data used in the identification of 19 and 20, a complete X-ray structure determination of 2,5-dimethyl-7,7-dicyanonorcaradiene was recently reported by Fritchie at du Pont.<sup>31</sup> He found that 19 crystallized in the orthorhombic space group  $P 2_1 2_1 2_1$  with four molecules in a cell having the dimensions  $a = 11.044$ ,  $b = 7.126$ ,  $c = 12.113$  Å. The molecule was found to have  $C_s$  symmetry with the cyclopropane ring inclined to the approximately planar cyclohexadiene ring by an angle of  $73^\circ$ . The measured cyclopropane bond lengths were 1.554, 1.558, and 1.501 Å as compared to carbon-carbon bond lengths in cyclopropane of  $1.510 \pm 0.002$  Å. This variation in bond lengths, Fritchie suggests, is indicative of the specific electronegativity or conjugative property of the gem-cyano group on the ring. The average length of bonds adjacent to the cyclopropane ring in 19 were found to be appreciably shorter than the average  $C_{sp^3} - C_{sp^2}$  bond length of 1.510 Å.<sup>33</sup> The angle of bond bending in the cyclopropane ring was estimated at  $20^\circ$ . In this crystallographic study, however, Fritchie reported that the  $\pi$  bonds associated with the cyclohexadiene ring and with the cyano groups could not be seen and also that it was doubtful that use of different  $\sigma$  bond form factors for the various carbon-carbon and carbon-nitrogen bonds would have been significant in this case. Nevertheless, this crystallographic study proves almost unequivocally the existence of a simple, stable norcaradiene structure.

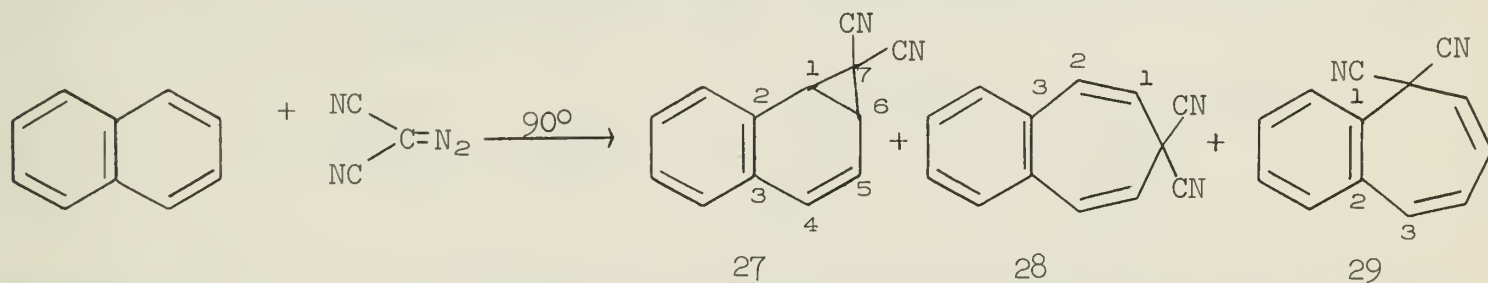
Berson<sup>34</sup> and coworkers in 1967 found that the thermolysis of dicyanodiazomethane toluene afforded a mixture of the three x-methyl-7,7-dicyanonorcaradienes (21)-( 23) and the three tolylmalononitriles (24)-( 26). The structural assignments of the





products were determined by spectroscopic methods and deuterium labelling studies. The norcaradienes were found to interconvert quite rapidly and prolonged heating resulted in appreciably aromatization. Aromatization was also observed during chromatographic separation attempts. Maximizing the reaction conditions to inhibit as much as possible aromatization and interconversion resulted in the isolation of 10-20% of 21 and total aromatics and 40-45% each of 22 and 23.

Ciganek<sup>23</sup> also studied the thermolysis of dicyanodiazomethane in a stirred naphthalene melt at 90°. A 50% yield of 7,7-dicyano-2,3-benzonorcaradiene (27) was obtained in addition to a combined 12% yield of 7,7-dicyano-3,4-benzocycloheptatriene (28) and 7,7-dicyano-1,2-benzocycloheptatriene (29). The nmr of 27 showed a four



proton multiplet at  $\tau$ 2.2-2.7, the two olefinic protons gave a doublet at  $\tau$ 3.03 and a quartet at  $\tau$ 3.77 ( $J_{4,5} = 10$  cps), and the cyclopropane protons gave a doublet at  $\tau$ 6.20 and a quartet at  $\tau$ 6.65 ( $J_{1,6} = 9$  cps;  $J_{5,6} = 5$  cps). Ultraviolet data also supported the norcaradiene structure. The structures of 28 and 29 were also deduced from their nmr spectra and ultraviolet data. In particular, the ultraviolet spectra of 28 and 29 were almost identical to that of the parent 3,4-benzocycloheptatriene (28  $\lambda_{\text{max}}$  in cyclohexane 228 m $\mu$  ( $\epsilon$ 46,000) and 257 m $\mu$  ( $\epsilon$ 5900); 3,4-benzocycloheptatriene  $\lambda_{\text{max}}$  in ethanol 228 m $\mu$  ( $\epsilon$ 44,000) and 256 m $\mu$  ( $\epsilon$ 5200)).<sup>35</sup> It is interesting to note that the nmr spectra of 28 and 29 show that the protons at C-1 and C-6 would give a signal at approximately  $\tau$ 4.0 for the hypothetical 7,7-dicyanocycloheptatriene, protons which, in the spectrum of 27, are found at  $\tau$ 6.20 and 6.65.<sup>23</sup>

#### THE ANOMALOUS STABILITY OF 7,7-DICYANONORCARADIENES

In order to offer an explanation to the puzzling question of the unusual stability of some of the 7,7-dicyanonorcaradienes discussed one must first examine the following facts.<sup>23</sup> The only reported stable, simple norcaradienes have two cyano groups substituted at the C-7 position. Replacement of one of these groups by a trifluoromethyl group results in the "destabilization" of the cycloheptatriene structure. No detectable concentrations of norcaradienes are found by substituting 7,7-dimethyl-, 7,7-bis(trifluoromethyl)-, 7-cyano-, or 7-carbethoxy groups for the 7,7-dicyano moiety. Two cyano groups stabilize the norcaradiene only if they are both in the seven position. Finally, a positive entropy change would be expected, a priori, for the isomerization of 7,7-dicyanonorcaradiene to the corresponding cycloheptatriene. Ciganek<sup>23,36</sup> advances three explanations for the unusual stability of 18. Two electron withdrawing cyano groups seem to be necessary at C-7 in norcaradiene in order for it to be stable but these particular substituents, as

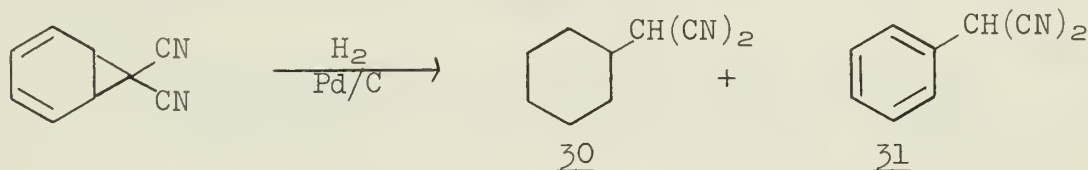




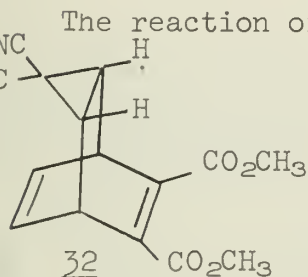
a result of their hybridization and electronegativity, would be expected to substantially destabilize the norcaradiene structure. However, the orbitals cyclopropane directs towards substituents are known to be quite high in s character and, according to Bent,<sup>37</sup> these orbitals would seek out electropositive substituents. Therefore, by consideration of the dipole-dipole interaction between two cyano groups one can see that Bent's statement actually accommodates a norcaradiene structure in the case of 18. Secondly, the presence of a gem-cyano group at C-7 would best be accommodated by a norcaradiene structure since the mutual repulsion of the cyano groups would tend to increase the NC-C-CN angle and therefore decrease the C1-C7-C6 angle. The frame work of the cycloheptatriene structure is less suited to satisfy this requirement than is the norcaradiene structure.<sup>31</sup> Finally, Ciganek has mentioned the possibility that formation of an internal charge-transfer complex between one cyano group and the planar diene system in norcaradiene may contribute to the relative stability of 18. Even though the dipole moment of 18 has been measured as 4.8 D, there is no indication of a charge transfer band in the ultraviolet spectrum. The position and intensity of  $\lambda_{\max}$  was found to be independent of solvent polarity. In addition, to invoke a charge-transfer complex stabilization of 18 one must also assume that one cyano group is not a sufficiently strong  $\pi$  acid in the absence of another electron withdrawing group on C-7 because of the instability of 7-cyanonorcaradiene.<sup>23</sup>

#### REARRANGEMENTS AND REACTIONS OF 7,7-DICYANONORCARADIENES

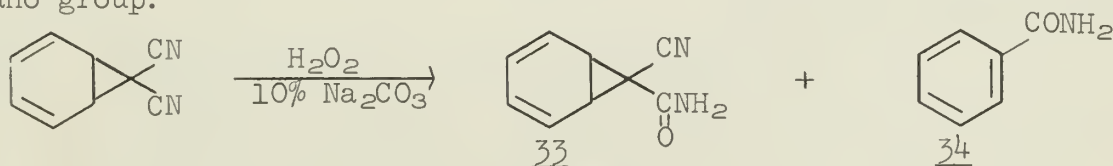
Catalytic hydrogenation<sup>37</sup> of 7,7-dicyanonorcaradiene on palladium in methanol resulted in appreciable reduction of the cyano groups. The only compounds formed in which the cyano groups were still present were cyclohexylmalononitrile (30) in 12% yield and traces of phenylmalononitrile (31). These products were identified on the basis of nmr and glpc data.



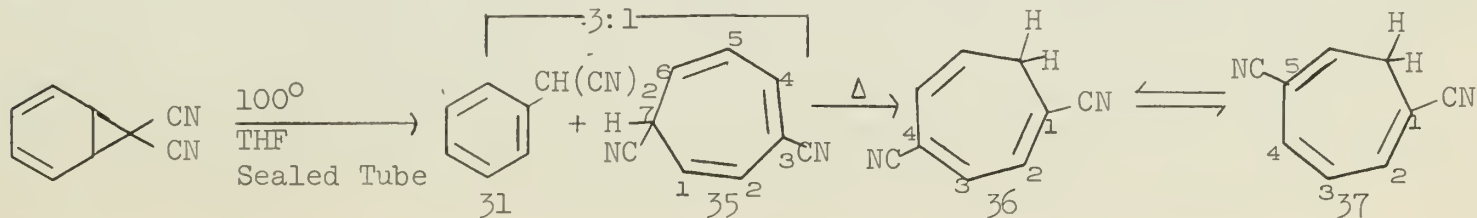
The reaction of 7,7-dicyanonorcaradiene with dimethylacetylenedicarboxylate at 100° formed a Diels-Alder adduct which was assigned structure 32 on the basis of nmr data. The anti configuration of the cyclopropane ring was assumed by analogy with the stereochemical assignments of the adducts of dimethylacetylenedicarboxylate to cycloheptatriene and its derivatives substituted in the seven position.<sup>38</sup>



Hydrolysis of 7,7-dicyanonorcaradiene by alkaline hydrogen peroxide afforded a 56% yield of 7-cyano-7-carbamidonorcaradiene (33) and a 16% yield of benzamide (34). Only one isomer of the two possible for 33 was present in the reaction products and no attempt was made to assign either the endo or exo configuration to the cyano group.



Thermolysis<sup>37</sup> of 7,7-dicyanonorcaradiene in a variety of solvents at 100° afforded phenylmalononitrile (31) and 3,7-dicyanocycloheptatriene (35); continued heating resulted in the isomerization of 35 to 1,4-dicyanocycloheptatriene (36) which was reported to be in equilibrium with, presumably, 1,5-dicyanocycloheptatriene (37). The

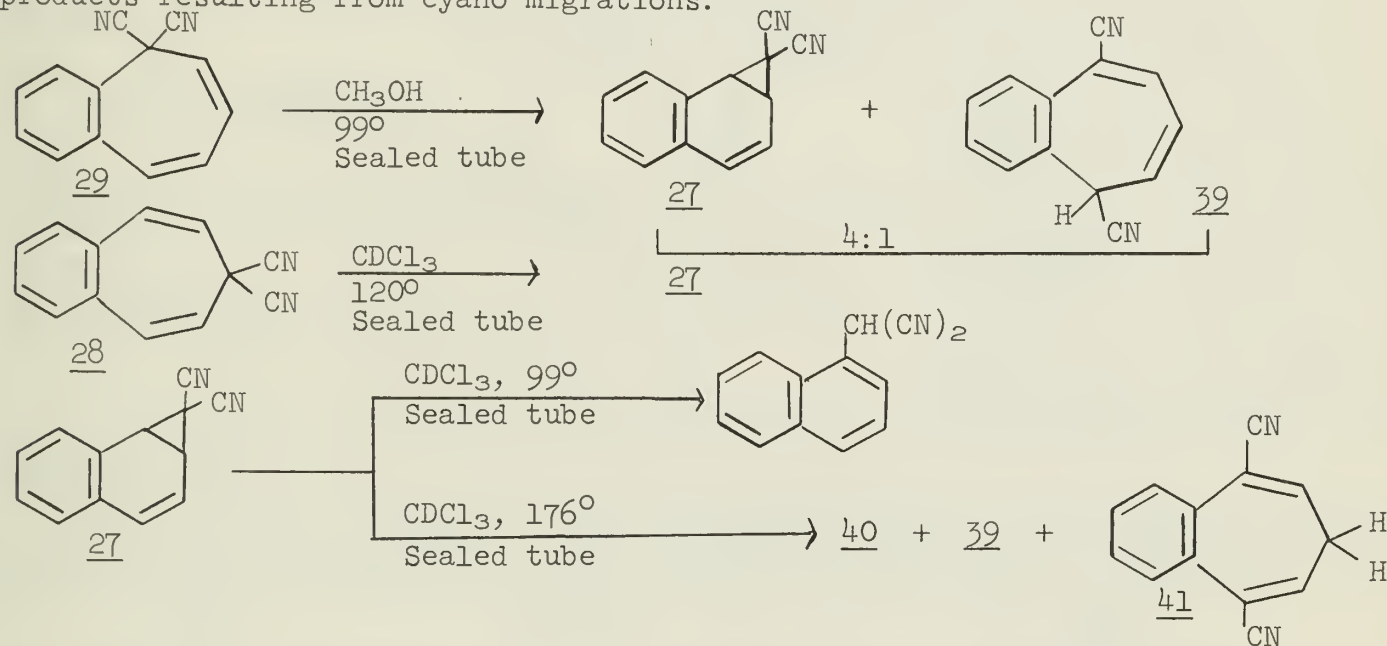




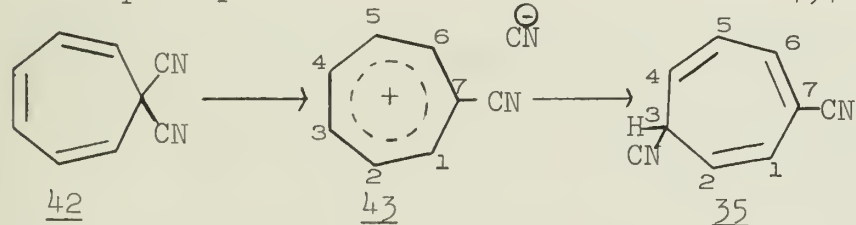
structure of 35 was assigned on the basis of its 100 Mc nmr spectrum. The structure of 36 was also deduced on the basis of nmr data; however, 37 was not isolated from the reaction mixture and its structural assignment was based solely on the nmr spectrum of the equilibrium mixture of 36 and 37. These cyano migrations were not found to occur in the thermolysis of the x-methyl-7,7-dicyanonorcaradienes, 21, 22, and 23 studied by Berson<sup>34</sup> or in the thermolysis of a mixture of 2,5-dimethyl- and 1,4-dimethyl-7,7-dicyanonorcaradiene, 19 and 20, studied by Ciganek.<sup>37</sup> Thermolysis of

this mixture at 130° gave as the sole product an 85% yield of 2,5-xylylmalononitrile (38) which was identified on the basis of its nmr spectrum and by its conversion to the known 2,5-xylylacetic acid.

However, the thermolysis of the dicyanocarbene-naphthalene adducts, 27, 28, and 29 again gave rise to products resulting from cyano migrations.<sup>37</sup>



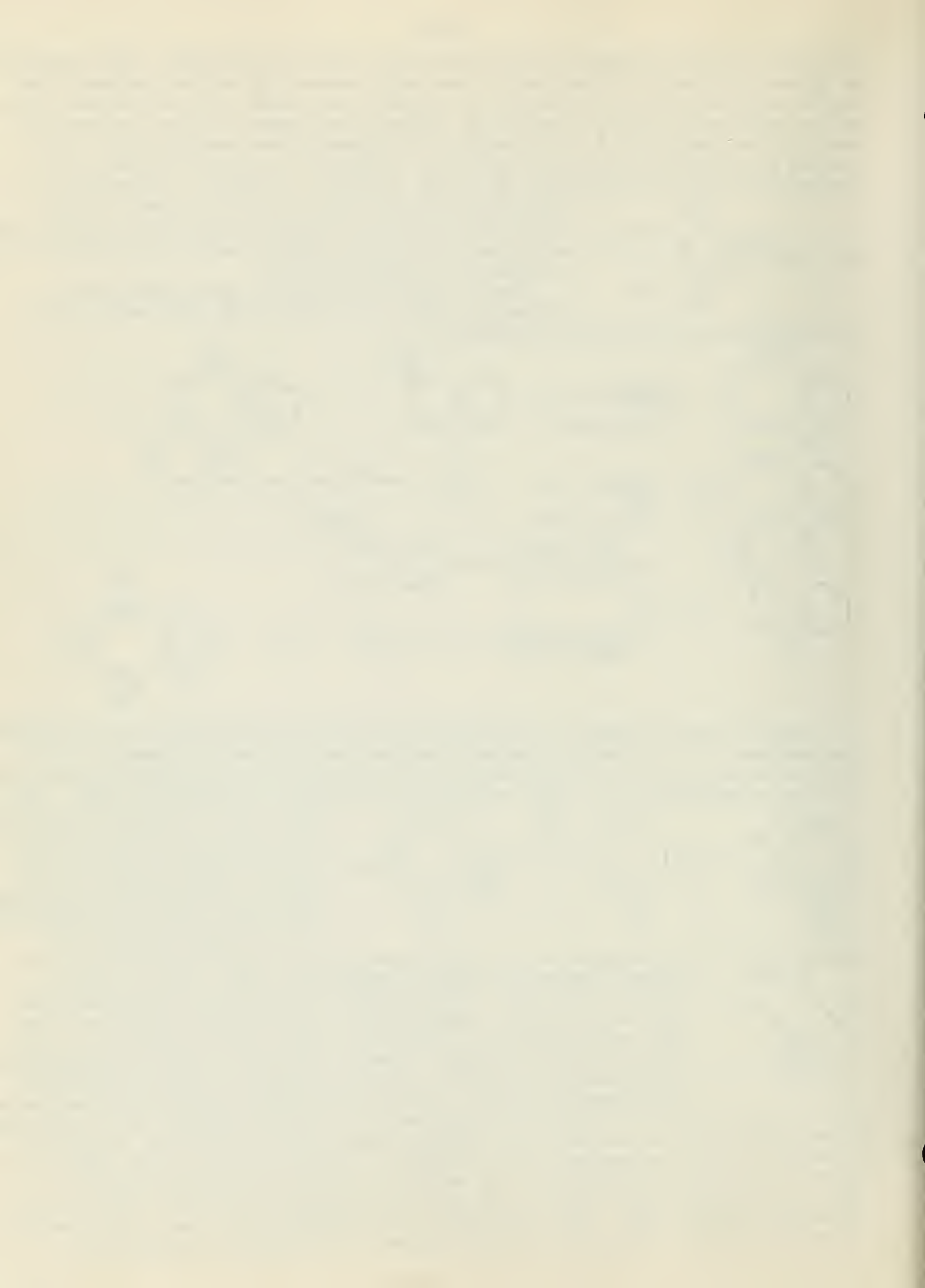
Three possible mechanistic interpretations for the isomerization of 7,7-dicyanonorcaradiene to 3,7-dicyanocycloheptatriene have been proposed by Ciganek.<sup>37</sup> The basic assumption in all of these interpretations is that 7,7-dicyanonorcaradiene exists in a rapid equilibrium with small amounts of 7,7-dicyanocycloheptatriene (42). The



ionization-recombination mechanism would involve initial formation of cyanotropilium cyanide (43) from 42. Recombination of the cyano anion at C-3 would give the observed 3,7-dicyanocycloheptatriene. One could also envision the

possibility of an intramolecular 1,5 shift mechanism that could either involve the bridged dipolar or diradical intermediate (44), or result from a concerted 1,5 shift. Evidence points against the ionization-recombination mechanism; Ciganek reports that various researchers<sup>39</sup> have found that mixtures of isomers are produced when tropylium ions are trapped with nucleophiles. However, only one isomeric cycloheptatriene, 35, is formed as an initial reaction product in the thermolysis of 7,7-dicyanonorcaradiene. Also, an ionization-recombination mechanism

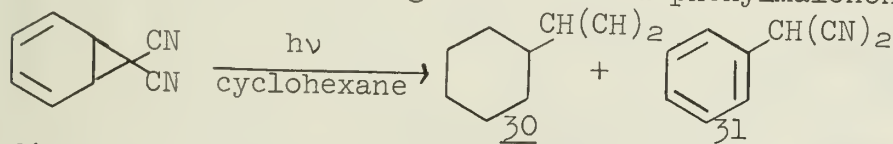
involving the formation of 43 would be expected to be highly dependent on the polarity of the solvent used in the reaction; however, changing the solvent from chloroform to methanol in the rearrangement of 7,7-dicyano-1,2-benzocycloheptatriene (29) to 3,7-dicyano-1,2-benzocycloheptatriene (39) results in a rate enhancement of only 4.2. This low enhancement also tends to discredit the mechanism postulating formation of the dipolar species (44). The thermolysis of 7,7-dicyanonorcaradiene in the presence of labelled cyanide ion would distinguish between the ionization-recombination



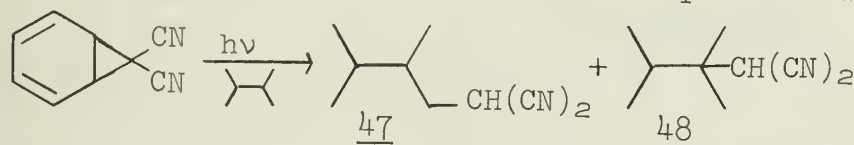


mechanism and the mechanism involving an intramolecular 1,5 shift, but 18 was found to react with the tetraethyl ammonium cyanide which was used as the source of the labelled cyanide ion. There is no evidence to discredit the mechanistic pathway involving the diradical species although Ciganek notes that there is no precedent for radical additions to nitrile groups.<sup>37</sup> A concerted 1,5 shift also cannot be ruled out by experimental evidence as a possible mechanism for the rearrangement although concerted shifts other than those for hydrogen have not been observed in cycloheptatrienes. Berson's<sup>40</sup> investigation of the thermal rearrangement of 3,7,7-trimethylcycloheptatriene showed no evidence of any 1,5 methyl shifts. However, the small steric requirements of the cyano group coupled with the fact that there is no substituent at or near the migration terminus would seem to lend credence to the possibility of a concerted 1,5 cyano shift.<sup>37</sup>

The photolysis<sup>37</sup> of 7,7-dicyanonorcaradiene in cyclohexane using a high pressure mercury lamp gave cyclohexylmalononitrile (30) in 60% yield in addition to a 14% yield of a mixture of starting material and phenylmalononitrile (31) as judged by nmr.



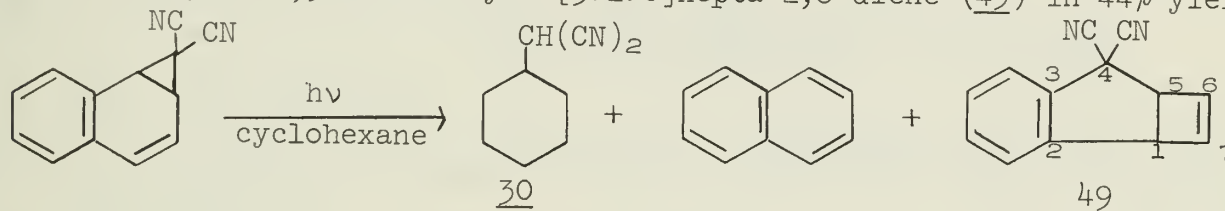
Changing the solvent to 2,3-dimethylbutane resulted in the formation of 2,3-dimethyl-1-butylnitrile (47) and 2,3-dimethyl-2-butylnitrile (48), each in 27% yield based on starting material not recovered. A 6% yield of unidentified products was also reported. The products can be



rationalized as being formed via a photolytic carbene transfer mechanism. It was found, in comparison, that the insertion products, 47 and 48, were formed

in approximately equal amounts from the thermolysis of dicyanodiazomethane in 2,3-dimethylbutane.

The photolysis of 7,7-dicyano-2,3-benzonorcaradiene in cyclohexane gave three isolable products identified as cyclohexylmalononitrile (22%), naphthalene (22%), and 4,4-dicyano-2,3-benzobicyclo[3.2.0]hepta-2,6-diene (49) in 44% yield. It was also



found that irradiation of 7,7-dicyano-1,2-benzocycloheptatriene in cyclohexane for 90 minutes gave an essentially quantitative yield of 49. The nmr of 49 showed a multiplet at  $\tau$ 2.2-2.6 (4H); a doublet ( $J = 2.6$  cps) split into doublets ( $J = 0.7$  cps) and split again into doublets ( $J = 0.3$  cps) centered at  $\tau$ 3.41 (1H); a doublet ( $J = 2.6$  cps) split into triplets ( $J = 0.9$  cps) centered at  $\tau$ 3.75 (1H); a doublet ( $J = 3.1$  cps) split again but poorly resolved at  $\tau$ 5.47 (1H); and a doublet ( $J = 3.1$  cps) split into doublets ( $J = 0.9$  cps) split into doublets ( $J = 0.3$  cps) centered at  $\tau$ 5.85 (1H).

## CONCLUSION

Although much work has been done on norcaradiene-cycloheptatriene systems in recent years, predicting which form will predominate in a given case or even convincingly rationalizing why a given form is favored in known examples remains a difficult challenge to ingenuity and resourcefulness, underscoring the present limits on understanding of these molecules. The facts presented in this seminar do indicate that stable norcaradienes can be formed without having to resort to synthetic tricks to force the molecule into a norcaradiene structure. The explanations for the peculiar stability of the 7,7-dicyanonorcaradienes and especially the necessity that both cyano groups be present to effect this stability are still open to question. Observations of the unusual cyano migrations in the rearrangements of 7,7-dicyanonorcaradienes open up a new area of research which could provide a deeper insight into the chemistry of norcaradienes.



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# MECHANISMS OF SOME OXIDATIONS WITH BROMINE

Reported by Bruce A. Morrison

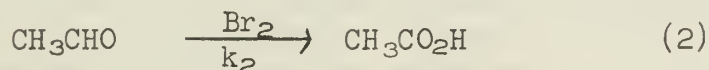
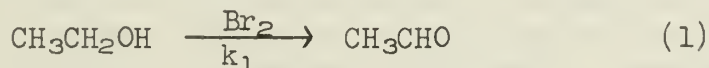
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## INTRODUCTION

The oxidizing ability of molecular bromine has a wide range of applications. Among these are the dehydration of tertiary alcohols,<sup>1</sup> the decarboxylation of silver carboxylate salts,<sup>2</sup> the selective phenol-peptide cleavage reaction,<sup>3,4</sup> the oxidative degradation of imidazoles,<sup>5</sup> the selective oxidation of carbohydrates to lactones, and the oxidation of alcohols and aldehydes. The structural and chemical relationship of carbohydrates with alcohols and aldehydes makes the mechanism of oxidation of these compounds of special interest. Kinetic studies of bromine oxidations have been somewhat briefly reviewed by Baker.<sup>6</sup>

## ALCOHOLS

Early investigators of the kinetics of the oxidation of ethanol to acetic acid<sup>7,8</sup> found that the reaction could be described as a two step process, equations 1 and 2.



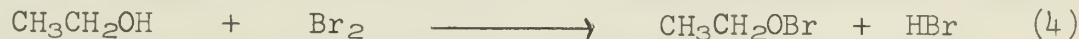
The ratio of the rate constants describing these reactions,  $k_1/k_2$ , was found to be on the order of 200.<sup>7,9</sup> This makes possible the study of the kinetics of the first step, oxidation of the alcohol, without significant interference from the aldehyde oxidation.

The rate of oxidation of ethanol as measured by the disappearance of bromine was found to be described by equation 3.<sup>7,8</sup> This rate was found to be independent

$$-d[\text{Br}_2]/dt = k_2[\text{Br}_2][\text{CH}_3\text{CH}_2\text{OH}] \quad (3)$$

of pH in the range pH 1-3.<sup>8</sup> The bromine concentration in equation 3 is that of free bromine; it does not include bromide ion or hypobromous acid, both of which were shown to be inactive as oxidizing agents in the pH range studied.

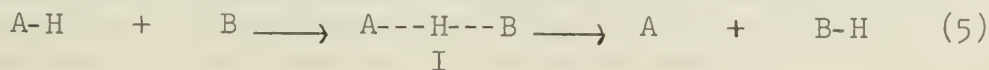
Kaplan<sup>9</sup> studied the oxidation of ethanol and ethanol-1, 1-d<sub>2</sub> by bromine in aqueous solution over a pH range of 2-10. He found a primary isotope effect,  $k_H/k_D$ , of 4.3 at 24.8° C for oxidation at pH 3. This led him to propose a mechanism involving rate-determining breaking of a C-H bond, possibly in the form of a hydride transfer to molecular bromine. The appreciable primary isotope effect rules out the rate-determining formation of a hypobromite ester, as shown in equation 4. The



formation of such an ester in the rate-determining step would be analogous to the mechanism of chromic acid oxidation of alcohols. The lack of pH or bromide dependence of the rate in acidic solution also rules out the possibility of equation 4 as a prior equilibrium. However, it should be noted that Deno and Potter<sup>10</sup> have pointed out a mechanism for hypobromite ester formation which also includes C-H bond-breaking, and therefore would not be excluded by the observed isotope effect. This work will be discussed below.

Kaplan also observed marked primary isotope effects,  $k_H/k_D$ , of 2.4 and 3.0 at pH 5.5 and 10.3 respectively. This indicates rate-determining C-H bond cleavage in more basic solutions. The observation of pH dependence of the rate above pH 3 reported by Farkas<sup>8</sup> caused Kaplan to speculate that a different or modified mechanism might be operating in more basic solutions.

Swain, Wiles, and Bader<sup>11</sup> have proposed a test for whether the species transferred in a rate-determining hydrogen loss is a proton or a hydride ion. The theory is based on an analysis of the molecular orbitals formed in the transition state for the transfer (I). The orbitals of A and B directed along the line of transfer, and the

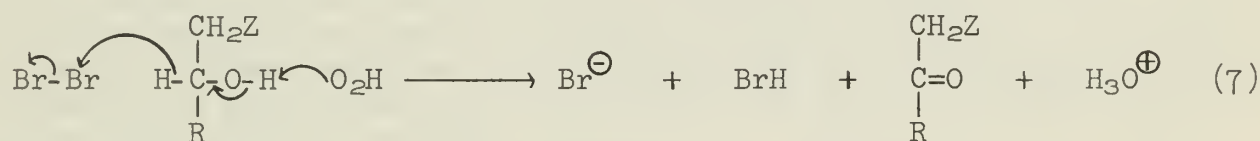
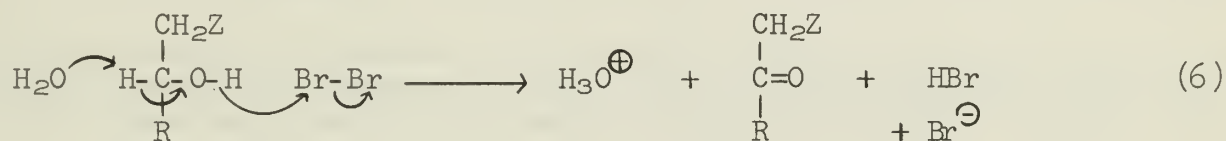




s-orbital of the hydrogen combine in the transition state into three molecular orbitals. If the species being transferred is a hydride ion, then the orbitals contributed by A and B will be electron deficient and the two electrons on hydrogen will provide the only electrons in the three molecular orbitals, thereby creating a short, non-polarizable bonding situation. If, however, the species being transferred is a proton, four electrons must be accommodated by the molecular orbitals in question, two from A in the original A-H bond, and two from the nucleophile B which is abstracting the proton. Only two of these electrons can be accommodated in the bonding orbital; therefore, two electrons go into a non-bonding orbital which has the effect of an antibonding orbital because of the electronic repulsion between other electrons on A and B. This situation leads to a weaker and more polarizable bond for the transfer of a proton.

Swain and his co-workers went on to predict that because of the effect just described, the nature of rate-determining hydrogen transfers can be elucidated by a study of the variation of primary deuterium kinetic isotope effects with the introduction of electronegative substituents on the hydrogen donating moiety. It was predicted that such substituents would markedly affect the isotope effect for proton transfer because of the more highly polarizable bonds involved, but that isotope effects for hydride transfer would be relatively unaffected. Presumably, an electronegative substituent would contribute to a greater degree of bond-breaking at the transition state, and consequently a larger isotope effect.

This hypothesis was applied to the oxidation of alcohols by aqueous bromine at pH 3 to decide between the possible mechanisms, 6 and 7. Mechanism 6 is analogous



to the presumed mechanism for chromic acid oxidation of alcohols and involves a rate-determining abstraction of a proton from carbon and of a hydride ion from oxygen. In equation 7 hydride is abstracted from carbon and a proton from oxygen. Oxidations were carried out on 2-propanol, 2-propanol-d, and 2-propan-2-d-ol, 1-fluoro-2-propanol, 1-fluoro-2-propanol-d, and 1 fluoro-2-propan-2-d-ol by aqueous bromine at 50° C. The results are summarized in Table I. According to Swain's hypothesis, these results

Table I. Isotope Effects for Oxidation of Substituted Isopropanols.

Deuterated Bond	Z	$k_{\text{H}}/k_{\text{D}}$
C-H	H	$2.94 \pm 0.1$
C-H	F	$2.83 \pm 0.1$
O-H	H	$1.49 \pm 0.1$
O-H	F	$2.06 \pm 0.1$

indicate a hydride abstraction from carbon and a proton transfer from oxygen--the situation described by the mechanism of equation 7.

Baker, Overend, and Rees<sup>12,13</sup> have studied the oxidation of substituted and unsubstituted cyclohexanols by bromine at 20° C. Aqueous solution was used for the unsubstituted compound, but mixed solvents employing tertiary alcohols in water were necessary for the substituted molecules. The rate of oxidation was measured both by the disappearance of bromine and the appearance of the cyclohexanones. The rate was found to be first-order in free bromine and first-order in alcohol.

The rate was found to be independent of pH from 0-5 and to decrease at pH 6-7. This is in marked contrast to the observations of other workers.<sup>8-10</sup> Two explanations

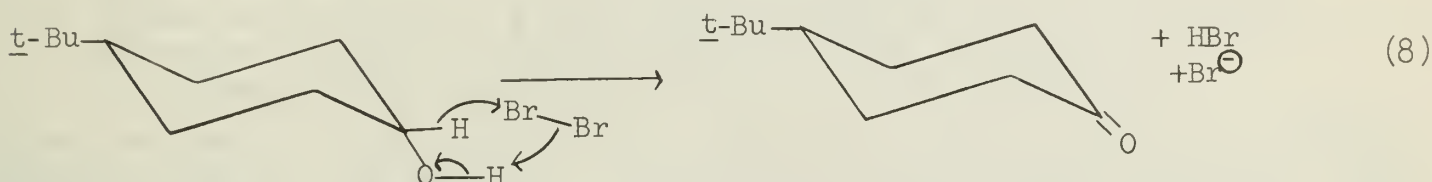






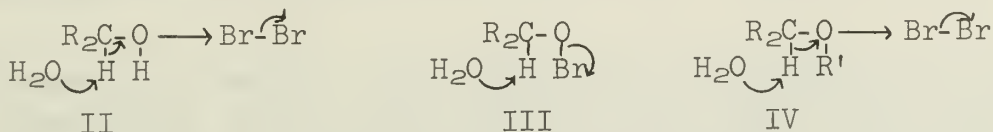
might be proposed. First, if the acid dependence usually observed in acyclic alcohols is attributable to a change in mechanism involving the formation of hypobromite ester intermediates in the rate-determining step, the steric requirements of the cyclohexanol system might be such that hypobromite formation is less favored at pH 6-7 and the effect observed is that of decreasing free bromine concentration. Alternatively, the effect could arise from the observation of the rate as measured by formation of cyclohexanone. The other investigators<sup>8,9</sup> all measured the rate entirely by bromine consumption. Consequently, were side reactions of the free bromine not involving oxidation of the alcohol to become important in more basic solution, the rate increase observed might not have been of the desired reaction.

Baker and his co-workers found that the oxidation rate was relatively independent of changes in the dielectric constant of the medium. In oxidations of cis and trans 4-t-butylcyclohexanol the cis compound reacted 30% faster than the trans. Similarly, 3 $\alpha$ -cholestanol reacted 18% faster than 3 $\beta$ -cholestanol. The small but definite preference of axial over equatorial hydroxyls is explained by the proposal of mechanism 8. The concerted cyclic transition state is favored by an observed independence of the



rate on changes in dielectric constant of the medium and by the small rate difference between axial and equatorial hydroxyl. A more polar transition state would be expected to exhibit rate enhancement in solvents of higher dielectric constant. The formation of a hypobromite ester would be expected to have a large steric requirement and to favor equatorial over axial hydroxyls. The existence of a prior equilibrium involving hypobromite ester formation is once again ruled out by the failure of the oxidation to exhibit pH dependence in the region pH 0-5. Such an effect could be operating in the region pH 6-7, however.

Deno and Potter have studied the oxidative cleavage of ethers with aqueous bromine<sup>14</sup> as well as the bromine oxidation of 2-propanol.<sup>10</sup> They propose a mechanism for alcohol oxidation involving the formation of a hypobromite ester following a rate-determining extraction of a proton from carbon. The transition states proposed for alcohol oxidation are shown as II and III below. Structure IV is the corresponding



proposed transition state for ether cleavage. The straight arrows in II and IV which connect oxygen and bromine are intended as two-electron transfers from the oxygen to the bromine. Deno and Potter feel that the mechanisms here are similar to those for cleavage and oxidation with chromic acid as described by Westheimer.<sup>15</sup> Venkatasubramanian and Thiagarajan<sup>16</sup> have pointed out that unlike the chromic acid case, where the rate of isopropanol oxidation is 1500 times as fast as isopropyl ether cleavage, the bromine reactions have the same rate constant. Deno and Potter demonstrated that the rate of isopropanol oxidation, though pH-invariant over the range 2-6, follows the concentration of hypobromous acid from pH 7-9. This concentration shows marked pH dependence as shown in Fig. 1.

Venkatasubramanian and Thiagarajan have studied the bromine oxidation of a series of 1-substituted isopropyl alcohols in 70% aqueous acetic acid at 40° C.<sup>16,17</sup> A Hammett plot of the log of rate constants against  $\sigma^*$  of the substituents gave a value for  $\rho^*$  of -2.6. They contend that this demonstration of decreasing rate with increasing electronegativity of the substituent favors the mechanisms proposed by Swain<sup>11</sup> and by Barker<sup>13</sup> which involve transfers of hydride ions from carbon. The hypobromite ester formation proposed by Deno<sup>10</sup> as the rate-determining step in acid-solution in-



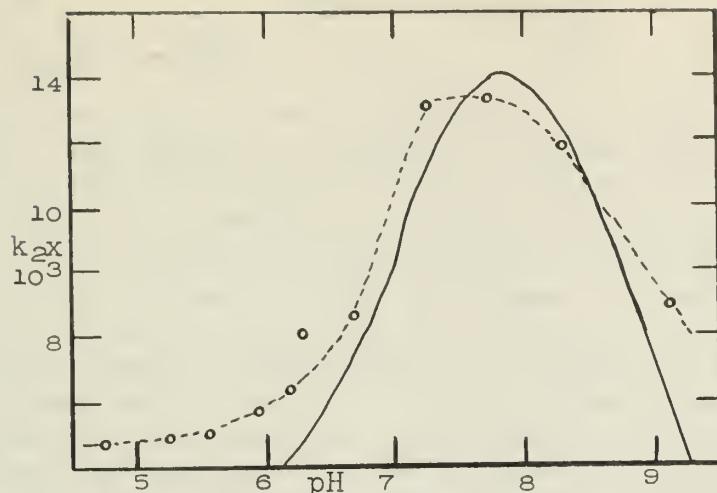
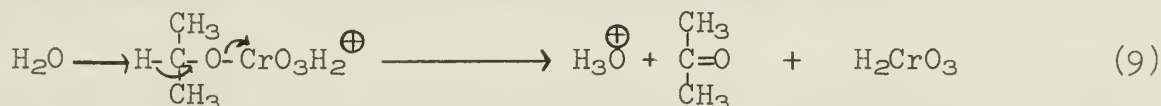


Figure 1. The dotted line with the experimental points (circles) are  $k_2$ ,  $\text{l. mole}^{-1} \text{sec}^{-1}$ , for the oxidation of 2-propanol by aqueous  $\text{Br}_2$  in the dark at  $25.0^\circ$ . The solid line is  $[\text{HOBr}]$  calculated for  $0.100 \text{ M NaBr}$  and  $1.80 \times 10^{-3} \text{ M}$  stoichiometric  $\text{HOBr}$  (or  $\text{Br}_2$ ) concentration. The value of  $1.80 \times 10^{-3} \text{ M}$  was chosen to bring the curves into closest coincidence since any offset vertically is of no significance.

volves the creation of an electron-rich center which would be expected to exhibit a positive  $\rho^*$  value. This data does not definitely rule out the formation of a hypobromite ester by another mechanism. The Deno transition state is not really analogous to the chromic acid ester formation proposed by Westheimer.<sup>15</sup> The latter involves the loss of hydrogen from oxygen in the formation step, with proton removal from carbon as part of the ester decomposition (see formula 9). Formation of the chromic



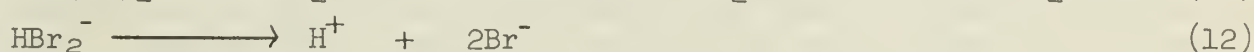
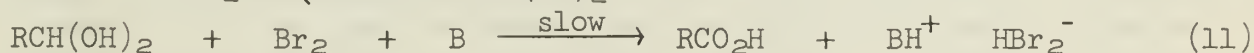
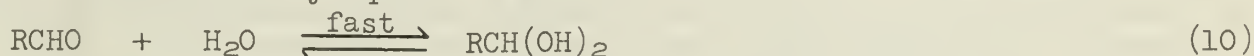
acid ester exhibits a  $\rho$  of  $-1.01$  in acid solution. The decomposition to ketone, however, has a positive  $\rho$ .<sup>18</sup>

Consequently, the mechanism proposed by Deno involving ester formation in acid solution is unlikely. However, his proposal of oxidation by hypobromous acid in basic solution is presently unchallenged. All of the other investigators have confined their experiments to acidic conditions.

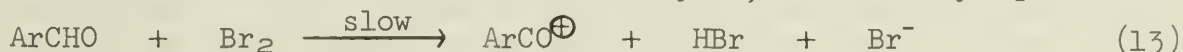
## ALDEHYDES

The oxidation of aldehydes with bromine has been summarized recently in some detail.<sup>18</sup> Consequently, only a brief summary of the most recent data will be presented.

Aliphatic aldehydes have been shown to exhibit primary kinetic isotope effects when substituted in the  $\alpha$ -position by deuterium.<sup>9</sup> They also exhibit an appreciable solvent isotope effect when oxidized by bromine in deuterium oxide.<sup>19,20</sup> These two factors indicate a rate determining step involving removal of hydrogens both from carbon and oxygen. The observation of general base catalysis<sup>21</sup> led to the hypothesis of the mechanism described by equations 10-12.

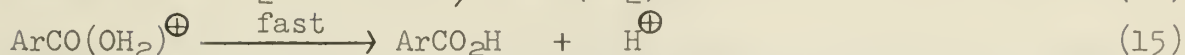
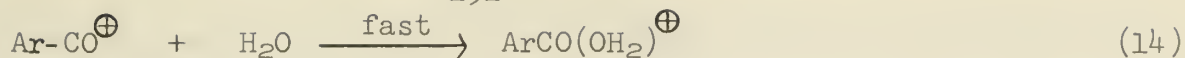


The hydrate of benzaldehyde has not been observed. In addition the solvent isotope effect for the bromine oxidation of benzaldehyde was only slightly more than  $\frac{1}{3}$  that of the aliphatic aldehydes.<sup>20</sup> These data led to the proposal of a different mechanism for the bromine oxidation of aromatic aldehydes, as shown by equations 13-15.



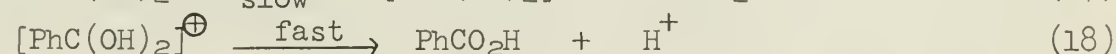
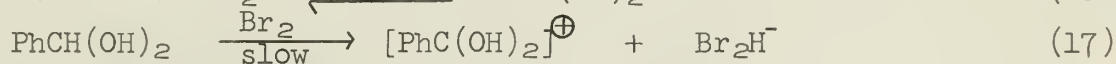
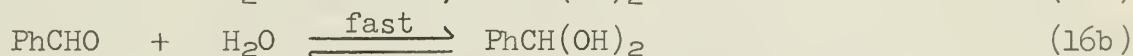
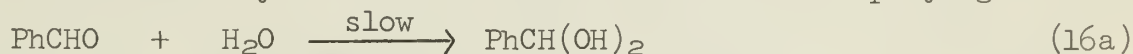






Here the rate-determining step is the abstraction of a hydride ion by molecular bromine.

Baker and Dahm<sup>22</sup> have recently presented evidence that benzaldehyde may also be oxidized by way of the hydrate mechanism. They studied the oxidation of substituted benzaldehydes in 50% aqueous acetic acid over the pH range 1-4. They found the rate to be first order in free bromine and first order in aldehyde. The rate increased with increasing pH in the region studied. The Hammett  $\rho$  value for meta-substitution gave a value of +0.17. This value is not consistent with the mechanism described by equations 13-15, which support a prediction of a relatively large negative  $\rho$  value. These data led Baker and Dahm to propose the mechanisms described by equations 16a, 16b, 17, and 18. Equations 16a and 16b are alternate proposals for the first step--the first being a slow reaction to form the hydrate of the aldehyde, the second involving a fast and reversible hydrate formation. The mechanism employing



16b, consisting of a slow hydride removal from a hydrate formed in a prior equilibrium, is favored by the observation of no reduction in the order of benzaldehyde in the rate expression with the addition of excess bromine. Both mechanisms are supported by the observation of increases in rate with increased water content in the medium. The observed base catalysis also supports either mechanism. However, the fact that the acetal of benzaldehyde has not been observed casts some doubt on this proposal.

## CARBOHYDRATES

The study of the mechanism of bromine oxidation of carbohydrates has been centered mainly on the reaction of  $\alpha$ - and  $\beta$ -D-glucose to form  $\delta$ -lactones. Both the reactants and the products would appear to indicate similarity to the oxidation of alcohols and aldehydes.

Early workers<sup>23-25</sup> reported that the oxidation of D-glucose by aqueous bromine is accomplished solely by the free bromine with no activity by bromide ion or hypobromous acid. It was reported<sup>24</sup> that the  $\beta$ -anomer is oxidized 35 times more readily than the  $\alpha$ -anomer.

Grover and Mehrota<sup>26</sup> studied the oxidation of glucose with bromine as a function of pH. They concluded that the rate of reaction paralleled the equilibrium concentration of hypobromous acid formed by the reaction of bromine with water. It was proposed that this observation could be traced to a mechanism for oxidation involving hypobromous acid as the oxidizing agent. This proposal is similar to the mechanism recently proposed by Deno and Potter<sup>10</sup> for the bromine oxidation of isopropanol in basic solution.

Perlmutter-Hayman and Persky<sup>27,28</sup> studied the bromine oxidation of anomerically equilibrated D-glucose as a function of pH and of added salt. They measured the rate of oxidation with hypobromous acid as the oxidizing agent. The rate was found to increase sharply as the reaction proceeded which was attributed to the liberation of molecular bromine.<sup>29</sup> It was thus contended that the specific rate of oxidation with hypobromous acid was unimportant with respect to that of bromine. However, experiments designed to exclude free bromine by precipitation with silver nitrate were complicated by catalysis of the reaction by added silver nitrate.

The rate of oxidation with bromine was found to be relatively independent of pH up to pH 3 at which point it began to increase rapidly and linearly up to the highest basicity studied (pH 6.9).<sup>27</sup> Perlmutter-Hayman and Persky propose that this pH dependence can be explained if it is assumed that the reactive species below pH 3 is the glucose molecule, but that above that pH the anion of the sugar becomes important. Perlmutter-Hayman and Weissman<sup>30</sup> have more recently proposed this phenomenon as a

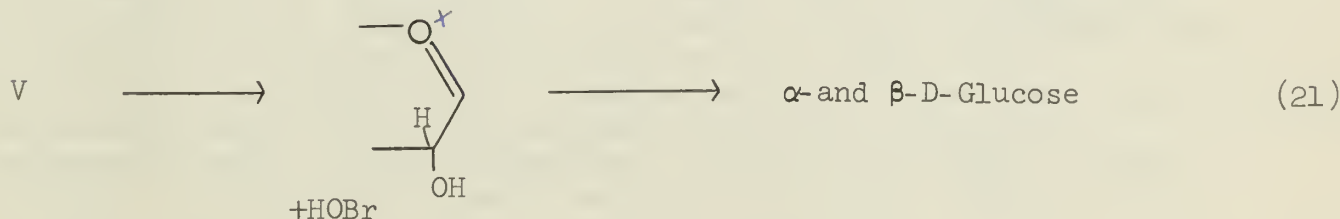
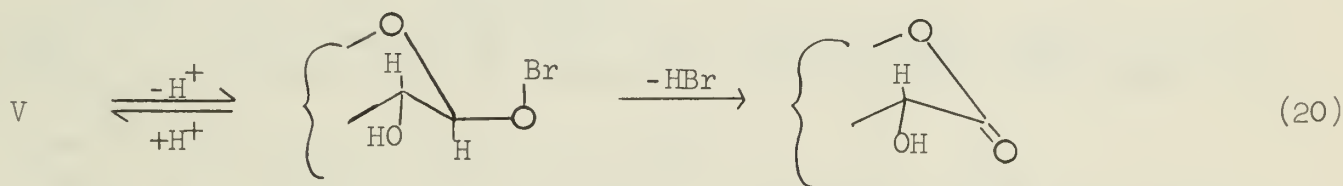
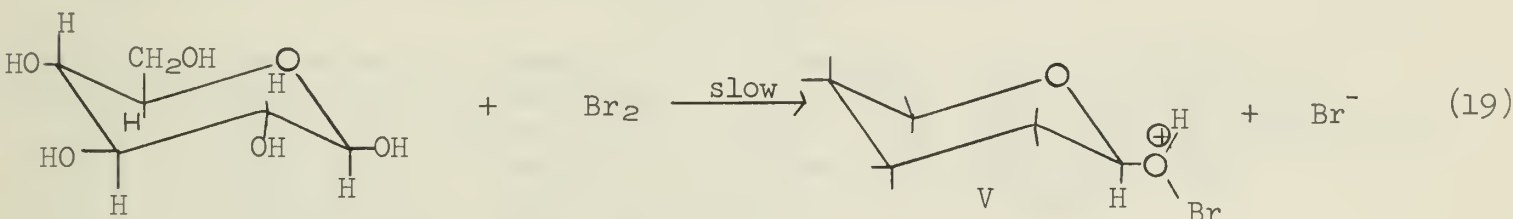


general explanation of the pH dependence of the bromine oxidation of alcohols and aldehydes.

Perlmutter-Hayman and Persky<sup>28</sup> also studied the bromine oxidation of anomerically equilibrated D-glucose as a function of ionic strength. They found that at pH 3.03 a strong positive salt effect was observed, but that at pH 1.5 the effect of increased ionic strength was negligible within experimental error. They contended that this observation confirmed their proposal that the pH dependence of the oxidation above pH 3 is caused by the anion of the sugar becoming the reactive species. The low  $pK_a$  of glucose in the pyranose form was discounted, despite the contention that the oxidation does not involve opening of the ring. Barker, Overend, and Rees have shown that for the anion to be the species responsible for the oxidation rate observed, the rate constant would have to be  $10^{11}$  times that for neutral glucose. No explanation is given for this enormous difference and no evidence is presented to support it.

Barker, Overend, and Rees investigated the bromine oxidation of pure samples of  $\alpha$ - and  $\beta$ -anomers of D-glucose.<sup>31,32</sup> They have shown that the oxidation reaction is complicated by anomerization to a far greater extent than had been previously reported. Their findings indicate that the measured rates for the oxidation of the  $\alpha$ -anomer which have been reported are almost entirely the rate of anomerization to the  $\beta$ -anomer. From studies of the pH dependence of the reaction of the  $\alpha$ -anomer the rate of oxidation can be estimated, since the anomerization is not pH dependent while the oxidation would be according to a mechanism analogous to that postulated for the  $\beta$ -anomer. Thus it was concluded that the rate of oxidation of the  $\beta$ -anomer must exceed that of the  $\alpha$ -anomer by a factor of at least 250.

Although the rate of oxidation is found to be inversely proportional to acidity, the effect of added bromide ion is to reduce the rate only to the extent that the concentration of the free bromine is reduced by conversion to tribromide ion. This result rules out a rate-determining step involving hypobromite ester formation, as well as a prior equilibrium to form such an ester, because the rate would then depend inversely on both acid and bromide concentration. To explain these observations, Barker and co-workers proposed the mechanism described by equations 19-21.<sup>32</sup> The path

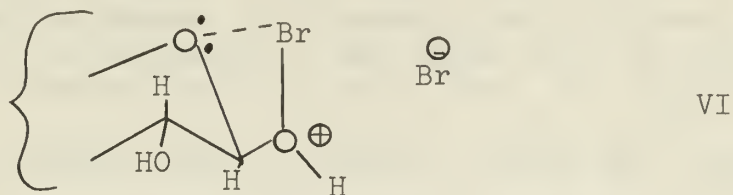


described in reaction 20 leads to the observed product and explains the large rate preference of the  $\beta$ -anomer over the  $\alpha$ -anomer. In the elimination of HBr, the  $\beta$ -compound can assume the proper configuration for trans elimination whereas such a configuration is highly strained in the corresponding intermediate in the oxidation of the  $\alpha$ -compound. The observed falling off of the rate of oxidation as the reaction proceeds is explained by postulation of the formation of relatively inert  $\alpha$ -D-glucose by the path defined in reaction 21.





It is thus observed that the oxidation of glucose follows a mechanism which is different from that of cyclohexanone.<sup>13</sup> Barker and co-workers explain this in terms of the interaction between the ring oxygen of glucose and the bromine atom in the hypobromite ester formed in reaction 19. This interaction is illustrated by structure VI.



Barker, Overend, and Rees<sup>32</sup> offer an alternative explanation for the pH dependence reported by Perlmutter-Hayman, and Persky. Barker and co-workers studied the oxidation of acetaldehyde as a function of pH in the range 1-5. They found that the rate was dependent on total bromine concentration, including tribromide ion, unlike alcohol oxidations which have been shown to depend only on free bromine. This led them to suggest that the oxidation involves a complex mechanism including oxidation of intermediates in the formation of the acetal which has been described as the reactive species.<sup>20</sup> Therefore, it is possible that in the range pH 0-3, glucose reacts as the open-chain aldehyde hydrate. Above pH 3 the oxidation of  $\beta$ -D-glucose, which is strongly retarded by acid, would begin to become important.

## SUMMARY

Oxidations with bromine in aqueous media have been shown to have several possible courses. In acid solution, alcohols, and aldehydes, in the form of their hydrate, appear to be oxidized by way of a rate-determining hydride removal from carbon with a synchronous proton removal from oxygen. In basic solution the mechanism may involve hypobromous acid and the formation of hypobromite esters. Sugars do not appear to share the same mechanism as free aldehydes and alcohols in general. The electronegative oxygen in the sugar ring appears to influence the mechanism and cause the formation of a protonated hypobromite ester intermediate.

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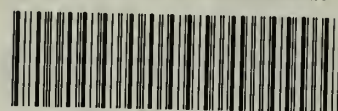








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